BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

2

Protection for the Hydroxyl Group Including 1,2- and 1,3-Diols

*Included in Reactivity Chart 1.

**Included in Reactivity Chart 2.

**Included in Reactivity Chart 2.

Hydroxyl groups are present in a number of compounds of biological and synthetic interest including nucleosides, carbohydrates, steroids, and the side chain of some amino acids. During oxidation, acylation, halogenation with phosphorus or hydrogen halides, or dehydration reactions of these compounds, a hydroxyl group must be protected. Ethers, acetals and ketals (cleaved by mild acidic hydrolysis), and esters (cleaved by basic hydrolysis) can be prepared to protect isolated hydroxyl groups; 1,2- and 1,3-diols can be protected as cyclic ethers (e.g., acetonides), cleaved by acidic hydrolysis, and as cyclic esters (e.g., carbonates and boronates), cleaved by basic hydrolysis. Simple *n*-alkyl ethers are stable compounds that are resistant to mild cleavage conditions. Benzyl and benzyl-

***Included in Reactivity Chart 3.

type ethers, however, can be cleaved by hydrogenolysis, silyl ethers by reaction with fluoride ion or by mild acidic hydrolysis, and various 2-substituted ethyl ethers by "assisted removal." Attempts to monoprotect a symmetrical diol as a polymer-supported ether have not been entirely satisfactory.[a]

ETHERS

In general an alcohol is converted to an ether by reaction with an alkylating agent in the presence of base; for example, see the preparation of methyl ethers, following compound **1**. Equation 1 illustrates a modification of this method. Iodotrimethylsilane (eq. 2) can be used to cleave a variety of ethers under mild conditions. (It also cleaves esters.[c,d])

(1) $\mathrm{ROH} + \mathrm{TlOEt} \xrightarrow[20°,\ \text{quant}]{C_6H_6} \mathrm{ROTl} \xrightarrow[20\text{–}60°]{\mathrm{R'X},\ CH_3CN} \mathrm{ROR'}$[b]

high yields

R'X = primary alkyl halides

(2) $\mathrm{ROR'} \xrightarrow[1\text{–}40\ \text{h},\ 25\text{–}80°]{Me_3SiI}$[c,d] ROH + HOR', high yields

Ethers that have been used extensively to protect alcohols are included in Reactivity Chart 1.[e]

[a] C. C. Leznoff, *Acc. Chem. Res.*, **11**, 327 (1978).

[b] H.-O. Kalinowski, D. Seebach, and G. Crass, *Angew. Chem., Inter. Ed. Engl.*, **14**, 762 (1975).

[c] M. E. Jung and M. A. Lyster, *J. Org. Chem.*, **42**, 3761 (1977).

[d] G. A. Olah, S. C. Narang, B. G. B. Gupta, and R. Malhotra, *J. Org. Chem.*, **44**, 1247 (1979).

[e] See also: C. B. Reese, "Protection of Alcoholic Hydroxyl Groups and Glycol Systems," in *Protective Groups in Organic Chemistry*, J. F. W. McOmie, Ed., Plenum, New York and London, 1973, pp. 95–143; H. M. Flowers, "Protection of the Hydroxyl Group," in *The Chemistry of the Hydroxyl Group*, S. Patai, Ed., Wiley-Interscience, New York, 1971, Vol. 10/2, pp. 1001–1044; C. B. Reese, *Tetrahedron*, **34**, 3143–3179 (1978), see pp. 3145–3150; V. Amarnath and A. D. Broom, *Chem. Rev.*, **77**, 183–217 (1977), see pp. 184–194.

1. Methyl Ether: $ROCH_3$, 1

Formation

A methyl ether can be prepared by the following conditions:

i. Me_2SO_4/NaOH, *n*-$Bu_4N^+I^-$, org solvent, 60–90% yield[a]
ii. CH_2N_2/silica gel, 0–10°, 100% yield[b]
iii. CH_2N_2/HBF_4, CH_2Cl_2, Et_3N, 25°, 1 h, 95% yield[c]
iv. MeI/solid KOH, DMSO, 20°, 5–30 min, 85–90% yield[d]

v. $(MeO)_2POH$/cat. TsOH, 90–100°, 12 h, 60% yield. Under these conditions, the C_5-double bond in a 3-hydroxy steroid does not shift to the C_4-position.[e]
vi. $Me_3O^+BF_4^-$, 3 days, 55% yield[f]
vii. carbohydrate + CF_3SO_2OMe, CH_2Cl_2, Py, 80°, 2.5 h, 85–90%[g]

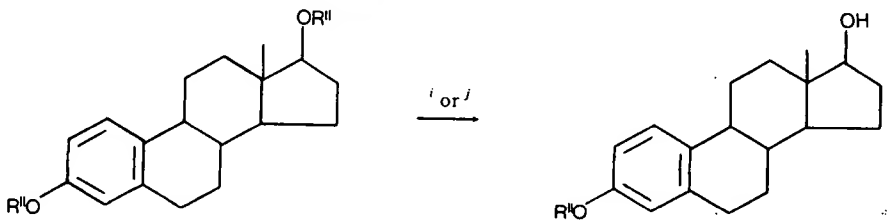
Cleavage

(1) $\mathrm{ROMe} \xrightarrow[25°,\ 6\ \text{h}]{Me_3SiI,\ CHCl_3}$[h] [$\mathrm{ROSiMe_3}$, 95%, + $\mathrm{MeOSiMe_3}$ + $\mathrm{RI} + \mathrm{MeI}] \xrightarrow{H_2O}$ ROH + MeOH, high yields

Selective cleavage, due to rate differences, is possible for triphenylmethyl, benzyl, or *t*-butyl ethers in the presence of methyl, ethyl, isopropyl, or cyclohexyl ethers. Dialkyl ethers are selectively cleaved (90–95% yield) in the presence of aryl alkyl ethers. A methyl ether is selectively cleaved in the presence of a methyl ester. Acetylenic, olefinic, carbonyl, and aryl halide compounds are stable.[h]

(2) $\mathrm{ROMe} \xrightarrow[70\text{–}80\%]{BF_3\cdot Et_2O,\ \mathrm{R'SH},\ 25°,\ \text{few days}}$[i] ROH

$\mathrm{ROMe} \xrightarrow[95\text{–}98\%]{AlX_3,\ EtSH,\ 25°,\ 0.5\text{–}3\ \text{h}}$[j] ROH



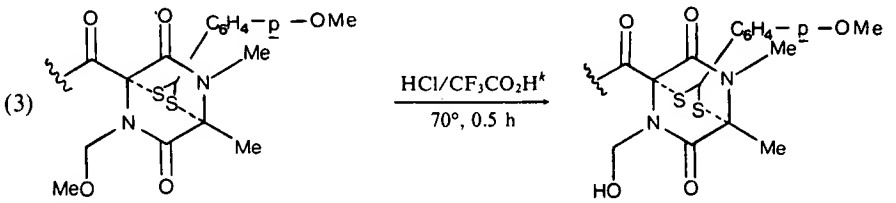
R'' = Me

R = $HS(CH_2)_2$, R = Me

93% yield[i]

R'' = H[j]

(3)



[a] A. Merz, *Angew. Chem., Inter. Ed. Engl.*, **12**, 846 (1973).
[b] K. Ohno, H. Nishiyama, and H. Nagase, *Tetrahedron Lett.*, 4405 (1979).
[c] M. Neeman and W. S. Johnson, *Org. Synth., Collect. Vol. V*, 245 (1973).
[d] R. A. W. Johnstone and M. E. Rose, *Tetrahedron*, **35**, 2169 (1979).
[e] Y. Kashman, *J. Org. Chem.*, **37**, 912 (1972).
[f] H. Meerwein, G. Hinz, P. Hofmann, E. Kroning, and E. Pfeil, *J. Prakt. Chem.*, **147**, 257 (1937).
[g] J. Arnarp and J. Lönngren, *Acta Chem. Scand., Ser. B*, **32**, 465 (1978).
[h] M. E. Jung and M. A. Lyster, *J. Org. Chem.*, **42**, 3761 (1977).
[i] M. Node, H. Hori, and E. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 2237 (1976).
[j] M. Node, K. Nishide, M. Sai, K. Ichikawa, K. Fuji, and E. Fujita, *Chem. Lett.*, 97 (1979).
[k] Y. Kishi, S. Nakatsuka, T. Fukuyama, and M. Havel, *J. Am. Chem. Soc.*, **95**, 6493 (1973).

Substituted Methyl Ethers

2. Methoxymethyl Ether (MOM Ether): $ROCH_2OCH_3$, 2

Formation

(1) $ROH + ClCH_2OMe \xrightarrow[i\text{-}Pr_2NH,\ 0°,\ 1\ h \rightarrow 25°,\ 8\ h,\ 86\%^b]{NaH,\ THF,\ 80\%^a\ or} \mathbf{2}$

ROH = allylic alcohol

(2) $ROH + CH_2(OMe)_2 \xrightarrow[25°,\ 30\ min,\ 95\%]{cat.\ P_2O_5,\ CHCl_3^c} \mathbf{2}$

Cleavage

(1) $ROCH_2OCH_3 \xrightarrow{HCl} ROH$

Trace concd HCl/MeOH, 62°, 15 min[d]

6 *M* HCl/aq THF, 50°, 6–8 h, 95% yield[e]

(2) $ArOCH_2OCH_3 \xrightarrow[reflux,\ 10\text{–}15\ min,\ 80\%]{50\%\ HOAc\text{–}cat.\ concd\ H_2SO_4^f} ArOH$

(3) $ROCH_2OCH_3 \xrightarrow[98\%]{PhSH,\ BF_3\cdot Et_2O^g} ROH$

(4) $ROCH_2OCH_3 \xrightarrow[25°]{Ph_3C^+BF_4^-,\ CH_2Cl_2^h} ROH$

[a] A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.*, **94**, 7827 (1972).
[b] G. Stork and T. Takahashi, *J. Am. Chem. Soc.*, **99**, 1275 (1977).
[c] K. Fuji, S. Nakano, and E. Fujita, *Synthesis*, 276 (1975).
[d] J. Auerbach and S. M. Weinreb, *J. Chem. Soc., Chem. Commun.*, 298 (1974).
[e] A. I. Meyers, J. L. Durandetta, and R. Munavu, *J. Org. Chem.*, **40**, 2025 (1975).
[f] F. B. Laforge, *J. Am. Chem. Soc.*, **55**, 3040 (1933).
[g] G. R. Kieczykowski and R. H. Schlessinger, *J. Am. Chem. Soc.*, **100**, 1938 (1978).
[h] T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, and Y. Kishi, *J. Am. Chem. Soc.*, **100**, 2933 (1978).

3. Methylthiomethyl Ether (MTM Ether): $ROCH_2SCH_3$, 3

Formation

(1) $ROH \xrightarrow[DME]{NaH} \xrightarrow[0°,\ 1\ h \rightarrow 25°,\ 1.5\ h,\ >86\%]{ClCH_2SCH_3/NaI^a} ROCH_2SCH_3$

ROH = primary alcohol

(2) $ROH \xrightarrow[20°,\ 12\ h,\ 80\text{–}90\%]{MeSCH_2I,\ DMSO,\ Ac_2O^b}$ or $\xrightarrow[20°,\ 1\text{–}2\ days,\ 80\%]{DMSO,\ Ac_2O,\ HOAc^c} \mathbf{3}$

ROH = primary, secondary, or tertiary alcohol

(3) $ROH \xrightarrow[22\text{–}80°,\ 4\text{–}24\ h,\ 60\text{–}80\%]{ClCH_2SMe,\ AgNO_3,\ Et_3N,\ C_6H_6^d} ROCH_2SCH_3$

Cleavage

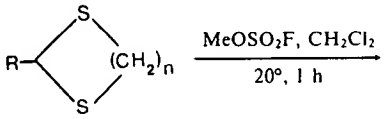
(1) $\mathbf{3} \xrightarrow[25°,\ 1\text{–}2\ h,\ 88\text{–}95\%]{HgCl_2,\ CH_3CN\text{–}H_2O^a}$ or $\xrightarrow[25°,\ 45\ min,\ 88\text{–}95\%]{AgNO_3,\ THF\text{–}H_2O,\ 2,6\text{-lutidine}^a} ROH$

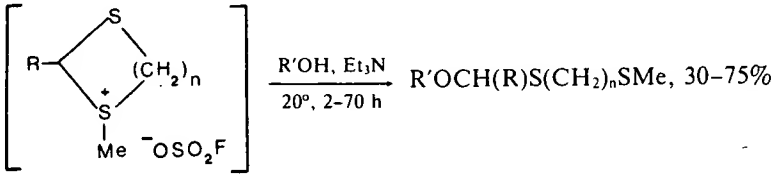
Methylthiomethyl ethers are stable to the mildly acidic conditions used to remove *O,O'*-acetonides or *O*-tetrahydropyranyl ethers. Silyl and *O*-tetrahydropyranyl ethers, and 1,3-dithianes are stable to the neutral cleavage conditions used here.[a]

(2) $\mathbf{3} \xrightarrow[heat,\ few\ h,\ 80\text{–}95\%]{MeI/acetone\text{–}H_2O,\ NaHCO_3^c} ROH$

ROH = primary, secondary, or tertiary alcohol

A variety of alcohols, R'OH, have been protected as hemithioacetals by reaction with a sulfonium salt, **a**[c]:





a

R' = *n*-Pr, *i*-Pr, Ph, Me_3SiCH_2, . . .

[a] E. J. Corey and M. G. Bock, *Tetrahedron Lett.*, 3269 (1975).
[b] K. Yamada, K. Kato, H. Nagase, and Y. Hirata, *Tetrahedron Lett.*, 65 (1976).
[c] P. M. Pojer and S. J. Angyal, *Aust. J. Chem.*, **31**, 1031 (1978).
[d] K. Suzuki, J. Inanaga, and M. Yamaguchi, *Chem. Lett.*, 1277 (1979).
[e] T. A. Hase and R. Kivikari, *Synth. Commun.*, **9**, 107 (1979).

4. Benzyloxymethyl Ether: $ROCH_2OCH_2C_6H_5$, 4

***Formation* (→) / *Cleavage* (←)[a]**

$$ROH \xrightarrow[10\text{–}20°,\ 12\ h,\ 95\%]{PhCH_2OCH_2Cl,\ EtN\text{-}i\text{-}Pr_2} \mathbf{4} \xleftarrow{Na/NH_3,\ EtOH} ROH$$

ROH = allylic alcohol

[a] G. Stork and M. Isobe, *J. Am. Chem. Soc.*, **97**, 6260 (1975).

5. *t*-Butoxymethyl Ether: $ROCH_2OC(CH_3)_3$, 5

***Formation* (→) / *Cleavage* (←)[a]**

$$ROH \xrightarrow[-20 \rightarrow 20°,\ 3\ h,\ 54\text{–}80\%]{ClCH_2O\text{-}t\text{-}Bu,\ Et_3N} \mathbf{5} \xleftarrow[20°,\ 48\ h,\ 85\text{–}90\%]{aq\ CF_3COOH} ROH$$

ROH = alkyl, benzylic, allylic alcohol

Compound **5** is stable to some acidic conditions (e.g., hot glacial acetic acid; aq HOAc, 20°; anhyd CF_3COOH, 20°).[a]

[a] H. W. Pinnick and N. H. Lajis, *J. Org. Chem.*, **43**, 3964 (1978).

6. 2-Methoxyethoxymethyl Ether (MEM Ether): $ROCH_2OCH_2CH_2OCH_3$, 6

***Formation*[a]**

(1) $RO^- + CH_3OCH_2CH_2OCH_2Cl \xrightarrow[0°,\ 10\text{–}60\ min,\ >95\%]{THF\ or\ DME} \mathbf{6}$

(2) $ROH + MEMN^+Et_3Cl^- \xrightarrow[reflux,\ 30\ min,\ >90\%]{CH_3CN} \mathbf{6}$

(3) $ROH + MEMCl \xrightarrow[25°,\ 3\ h,\ quant]{EtN\text{-}i\text{-}Pr_2,\ CH_2Cl_2} \mathbf{6}$

***Cleavage*[a]**

$$\mathbf{6} \xrightarrow[25°,\ 2\text{–}10\ h,\ 90\%]{ZnBr_2,\ CH_2Cl_2} \text{or} \xrightarrow[0°,\ 20\ min,\ 95\%]{TiCl_4,\ CH_2Cl_2} ROH$$

Compound **6** was designed to protect primary, secondary, or tertiary alcohols with formation and cleavage under aprotic conditions. MEM ethers are stable to mild acidic hydrolysis (e.g., HOAc–H_2O, 35°, 4 h; cat. TsOH, MeOH, 23°, 3 h), conditions that cleave tetrahydropyranyl and silyl (including *t*-butyldimethylsilyl) ethers.[a]

Compound **6** can be cleaved by fluoroboric acid (HBF_4, CH_2Cl_2, 0°, 3 h, 50–60% yield).[b]

[a] E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Lett.*, 809 (1976).
[b] N. Ikota and B. Ganem, *J. Chem. Soc., Chem. Commun.*, 869 (1978).

7. 2,2,2-Trichloroethoxymethyl Ether: $ROCH_2OCH_2CCl_3$, 7

***Formation*[a]**

(1) $RO^- + Cl_3CCH_2OCH_2Cl \xrightarrow[5\ h,\ 70\text{–}90\%]{LiI/THF} \mathbf{7}$

(2) $ROH + Cl_3CCH_2OCH_2Cl \xrightarrow[30\text{–}60\%]{EtN\text{-}i\text{-}Pr_2,\ CH_2Cl_2} 7$

Cleavage[a]

(1) $7 \xrightarrow[\text{reflux, 97\%}]{Zn\text{–}Cu \text{ or } Zn\text{–}Ag/MeOH} ROH$

(2) $7 \xrightarrow[\text{reflux, 4 h, 90–100\%}]{Zn/MeOH,\ HOAc,\ Et_3N} ROH$

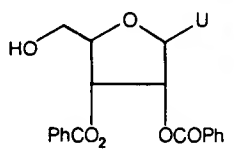
(3) $7 \xrightarrow{Li/NH_3} ROH$

Methoxymethyl ethers are stable to these cleavage conditions.[a]

[a] R. M. Jacobson and J. W. Clader, *Synth. Commun.*, **9**, 57 (1979).

8. Bis(2-chloroethoxy)methyl Ether: $ROCH(OCH_2CH_2Cl)_2$, 8

Formation (→) / ***Cleavage*** (←)[a]



$\xrightarrow[100°,\ 10\text{ min to }2\text{ h, }76\%]{HC(OCH_2CH_2Cl)_3}$ **8a** $\xleftarrow[20°,\ 1\text{ h}]{80\%\ HOAc}$

In this synthesis an acetal or unsubstituted ortho ester was too labile to acidic hydrolysis.[a]

[a] T. Hata and J. Azizian, *Tetrahedron Lett.*, 4443 (1969).

2-(Trimethylsilyl)ethoxymethyl Ether (SEM Ether): $ROCH_2OCH_2CH_2Si(CH_3)_3$, A

Formation[a]

$ROH + Me_3SiCH_2CH_2OCH_2Cl \xrightarrow[35\text{–}40°,\ 1\text{–}5\text{ h, }86\text{–}100\%]{EtN\text{-}i\text{-}Pr_2,\ CH_2Cl_2} RO\text{—}SEM$

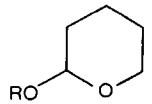
Cleavage[a]

$RO\text{—}SEM \xrightarrow[45°,\ 8\text{–}12\text{ h, }85\text{–}96\%]{n\text{-}Bu_4N^+F^-,\ THF \text{ or } HMPA} ROH$

ROH = primary, secondary, tertiary, aromatic alcohols

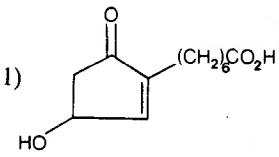
A SEM ether is stable to acetic acid ($HOAc/H_2O/THF$, 45°, 7 h) and to BuLi.[a]

[a] B. H. Lipshutz and J. J. Tegram, *Tetrahedron Lett.*, **21**, 3343 (1980).

9. Tetrahydropyranyl Ether (THP Ether):  , 9

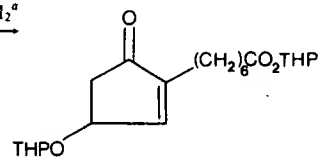
Since an asymmetric center is formed when a THP ether is prepared, the product may contain a mixture of diastereomers. No new asymmetric center is formed by reaction of an alcohol with 5,6-dihydro-4-methoxy-2*H*-pyran (e.g., see compound **12**).

Formation (→) / ***Cleavage*** (←)

(1) 

$\xrightarrow[20°,\ 1.5\text{ h, }100\%]{\text{dihydropyran, TsOH, } CH_2Cl_2[a]}$

$\xleftarrow[45°,\ 3.5\text{ h}]{HOAc,\ THF\text{–}H_2O\ (4:2:1)[a]}$



(2) $\xrightarrow[20°,\ 4\text{ h, }94\text{–}100\%]{\text{dihydropyran, PPTS, } CH_2Cl_2[b]}$

ROH ROTHP

$\xleftarrow[55°,\ 3\text{ h, }95\text{–}100\%]{PPTS,\ EtOH\ (pH\ 3.0)[b]}$

PPTS = pyridinium *p*-toluenesulfonate

An epoxide is stable to formation of compound **9** under these conditions.[b]

(3) $\xrightarrow[1\text{–}2\text{ h, }95\%]{\text{dihydropyran, Amberlyst H-15, hexane}[c]}$

ROH ROTHP

$\xleftarrow[45°,\ 1\text{ h, }95\%]{Amberlyst\ H\text{-}15,\ MeOH[c]}$

Amberlyst H-15 is an ion-exchange resin that contains $-SO_3H$ substituents.

Compound **9** has been cleaved by treatment with methanol/Dowex-50W-X8 (25°, 1 h, 99% yield).[d]

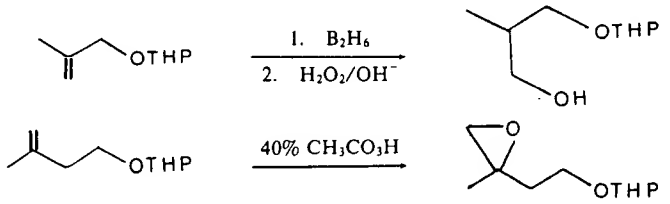
Cleavage

(1) Glyceride-OTHP $\xrightarrow[90°,\ 2\ h,\ 80\text{–}95\%]{\text{boric acid, EtOCH}_2\text{CH}_2\text{OH}^{e}}$ ROH

(2) ROTHP $\xrightarrow[25°,\ 1\ h,\ 94\%]{\text{TsOH, MeOH}^{f}}$ ROH

ROH = a primary, allylic alcohol

Explosions have been reported on distillation of compounds containing a tetrahydropyranyl ether after a reaction with $B_2H_6/H_2O_2\text{–}OH^-$, and with 40% CH_3CO_3H:



It was thought that the acetal might have reacted with peroxy reagents, forming explosive peroxides. It was suggested that this could also occur with compounds such as tetrahydrofuranyl acetals, 1,3-dioxolanes, and methoxymethyl ethers.[g]

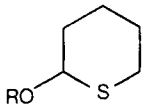
[a] K. F. Bernady, M. B. Floyd, J. F. Poletto, and M. J. Weiss, *J. Org. Chem.*, **44**, 1438 (1979).
[b] M. Miyashita, A. Yoshikoshi, and P. A. Grieco, *J. Org. Chem.*, **42**, 3772 (1977).
[c] A. Bongini, G. Cardillo, M. Orena, and S. Sandri, *Synthesis*, 618 (1979).
[d] R. Beier and B. P. Mundy, *Synth. Commun.*, **9**, 271 (1979).
[e] J. Gigg and R. Gigg, *J. Chem. Soc. C*, 431 (1967).
[f] E. J. Corey, H. Niwa, and J. Knolle, *J. Am. Chem. Soc.*, **100**, 1942 (1978).
[g] A. I. Meyers, S. Schwartzman, G. L. Olson, and H.-C. Cheung, *Tetrahedron Lett.*, 2417 (1976).

10. 3-Bromotetrahydropyranyl Ether: RO-3-bromotetrahydropyranyl, 10

Compound **10** was prepared from a C_{17}-hydroxy steroid and 2,3-dibromopyran (Py/C_6H_6, 20°, 24 h); it was cleaved by zinc/ethanol.[a]

[a] A. D. Cross and I. T. Harrison, *Steroids*, **6**, 397 (1965).

11. Tetrahydrothiopyranyl Ether:

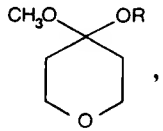


, **11**

Compound **11** was prepared from a C_3-hydroxy steroid and dihydrothiopyran ($CF_3COOH/CHCl_3$, 35% yield); it can be cleaved under neutral conditions ($AgNO_3$, aq acetone, 85% yield).[a]

[a] L. A. Cohen and J. A. Steele, *J. Org. Chem.*, **31**, 2333 (1966).

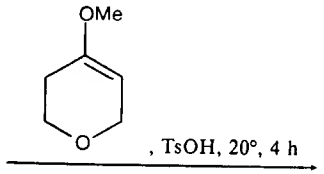
12. 4-Methoxytetrahydropyranyl Ether:



, **12**

Protection of an alcohol as compound **12** avoids the formation of an asymmetric center that occurs when a tetrahydropyranyl ether is formed (e.g., see compound **9**). This ether (**12**) is used extensively in oligonucleotide syntheses.

***Formation* (→) / *Cleavage* (←)[a]**



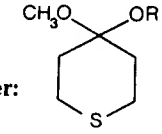
ROH **12**

$\xleftarrow{\text{0.01 } N \text{ HCl, 1 h}}$

ROH = uridine, $t_{1/2}$ = 24 min[a]

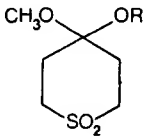
[a] C. B. Reese, R. Saffhill, and J. E. Sulston, *J. Am. Chem. Soc.*, **89**, 3366 (1967).

13. 4-Methoxytetrahydrothiopyranyl Ether:



, **13**

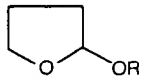
14. 4-Methoxytetrahydrothiopyranyl Ether *S,S*-Dioxide:



, **14**

Compound **13**, used in nucleotide syntheses, is hydrolyzed by acid 5 times faster than the oxygen analog (e.g., compound **12**). A sulfone, **14**, prepared from compound **13** by oxidation with *m*-$ClC_6H_4CO_3H$, is hydrolyzed 2000 times more slowly than the oxygen analog, **12**.[a]

[a] J. H. van Boom, P. van Deursen, J. Meeuwse, and C. B. Reese, *J. Chem. Soc., Chem. Commun.*, 766 (1972).

15. Tetrahydrofuranyl Ether:  , 15

Formation

(1) ROH + [tetrahydrofuran $\xrightarrow[25°,\ 0.5\ h,\ 85\%]{SO_2Cl_2/THF}$] $\xrightarrow[30\ min,\ 82\text{–}98\%]{Et_3N}$ **15**[a]

(2) ROH + Ph_2CHCOO-2-tetrahydrofuranyl $\xrightarrow[20°,\ 30\ min,\ 90\text{–}99\%]{1\%\ TsOH,\ CCl_4}$ **15**[a,b]

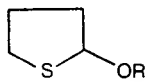
Cleavage

(1) **15** $\xrightarrow[25°,\ 30\ min,\ 90\%]{HOAc\text{-}H_2O\text{-}THF\ (3:1:1)^a}$ or $\xrightarrow[25°,\ 10\ min,\ 50\%]{0.01\ N\ HCl/THF\ (1:1)^a}$ ROH

(2) **15** $\xrightarrow[25°,\ 3\ h,\ 90\%]{pH\ 5^a}$ ROH

The authors report[a] that formation of compound **15** by reaction with 2-chlorotetrahydrofuran (eq. 1, ***Formation***) avoids a laborious procedure[c] that is required when dihydrofuran is used. The tetrahydrofuranyl ester (used in eq. 2, ***Formation***) is reported[a] to be a readily available, stable solid. A tetrahydropyranyl ether is not cleaved at pH 5 (eq. 2, ***Cleavage***).[a]

[a] C. G. Kruse, F. L. Jonkers, V. Dert, and A. van der Gen, *Recl. Trav. Chim. Pays-Bas*, **98**, 371 (1979).
[b] C. G. Kruse, E. K. Poels, F. L. Jonkers, and A. van der Gen, *J. Org. Chem.*, **43**, 3548 (1978).
[c] E. L. Eliel, B. E. Nowak, R. A. Daignault, and V. G. Badding, *J. Org. Chem.*, **30**, 2441 (1965).

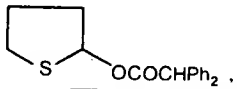
16. Tetrahydrothiofuranyl Ether:  , 16

Formation (→) / ***Cleavage*** (←)

(1) $\xrightarrow[reflux,\ 6\ days,\ 75\%]{dihydrothiofuran/CHCl_3,\ CF_3CO_2H^a}$

ROH **16**

$\xleftarrow[boil,\ few\ min,\ 90\%]{AgNO_3,\ aq\ acetone^a}$

(2)  $\xrightarrow[20°,\ 5\ h,\ 85\text{–}95\%]{OCOCHPh_2\ ,\ cat.\ TsOH,\ CHCl_3^b}$

ROH **16**

$\xleftarrow[25°,\ 10\ min,\ quant]{HgCl_2,\ CH_3CN\text{–}H_2O^b}$

Tetrahydrothiofuranyl ethers are used in ribonucleotide syntheses since they can be removed under neutral conditions, avoiding the alkaline conditions that cleave esters and acidic conditions that cleave tetrahydropyranyl ethers.[a]

Tetrahydrothiofuranyl ethers decompose above 100°.[b]

[a] L. A. Cohen and J. A. Steele, *J. Org. Chem.*, **31**, 2333 (1966).
[b] C. G. Kruse, E. K. Poels, F. L. Jonkers, and A. van der Gen, *J. Org. Chem.*, **43**, 3548 (1978).

Substituted Ethyl Ethers

17. 1-Ethoxyethyl Ether: $ROCH(OC_2H_5)CH_3$, 17

Formation

ROH + $CH_2{=}CHOEt$ $\xrightarrow{anhyd\ HCl^a}$ or $\xrightarrow[25°,\ 1\ h]{TsOH\cdot H_2O^b}$ **17**

ROH = nucleosides[a]; maytansinoid precursor[b]

Cleavage

17 $\xrightarrow[20°,\ 2\ h,\ 100\%]{5\%\ HOAc^a}$ or $\xrightarrow[0°,\ 100\%]{0.5\ N\ HCl/THF^b}$ ROH

Compound **17** was used in preference to a THP ether (i.e. compound **9**) in nucleotide syntheses since **17** is more readily cleaved by acidic hydrolysis (e.g., **17**: 100% yield, no isomerization; **9**: 37% yield, some isomerization).[a]

[a] S. Chládek and J. Smrt, *Chem. Ind. (London)*, 1719 (1964).
[b] A. I. Meyers, D. L. Comins, D. M. Roland, R. Henning, and K. Shimizu, *J. Am. Chem. Soc.*, **101**, 7104 (1979).

18. 1-Methyl-1-methoxyethyl Ether: $ROC(OCH_3)(CH_3)_2$, 18

***Formation* (→) / *Cleavage* (←)**[a]

$$ROH \underset{20°,\ 10\ min}{\overset{20\%\ HOAc}{\longleftarrow}} \mathbf{18} \underset{20°,\ 30\ min,\ 100\%}{\overset{CH_2{=}C(Me)OMe,\ cat.\ POCl_3}{\longrightarrow}}$$

ROH = an allylic alcohol used in prostaglandin model studies

[a] A. F. Klug, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.*, **94**, 7827 (1972).

19. 1-(Isopropoxy)ethyl Ether: $ROCH(CH_3)OCH(CH_3)_2$, 19

Compound **19** was prepared from a cyanohydrin and isopropyl vinyl ether (cold, trace HCl); it was cleaved by acidic hydrolysis (1 *N* HCl, warm, 30 min).[a]

[a] B. Tchoubar, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **237**, 1006 (1953).

20. 2,2,2-Trichloroethyl Ether: $ROCH_2CCl_3$, 20

Compound **20**, prepared to protect a hydroxyl group in a carbohydrate, is cleaved[a] by Zn/HOAc, NaOAc (3 h, 92% yield).

[a] R. U. Lemieux and H. Driguez, *J. Am. Chem. Soc.*, **97**, 4069 (1975).

21. 2-(Phenylselenyl)ethyl Ether: $ROCH_2CH_2SeC_6H_5$, 21

Compound **21** has been prepared from an alcohol and the ethyl bromide ($AgNO_3$, CH_3CN, 20°, 10–15 min, 80–90% yield); it is cleaved by oxidation (H_2O_2, 1 h; O_3; or IO_4^-), followed by acidic hydrolysis (dil HCl, 65-70% yield).[a]

[a] T.-L. Ho and T. W. Hall, *Synth. Commun.*, **5**, 367 (1975).

22. *t*-Butyl Ether: $ROC(CH_3)_3$, 22

A *t*-butyl group is used for selective protection of primary hydroxyl groups.

Formation

$$ROH + CH_2{=}CMe_2 \xrightarrow{cat.} \mathbf{22},\ \text{high yields}$$

cat. = concd H_2SO_4[a]; BF_3/H_3PO_4[b]

Cleavage

Compound **22** is cleaved by the following conditions:

i. Anhyd CF_3COOH, 0–20°, 1–16 h, 80–90%[a,b]
ii. HBr/HOAc, 20°, 30 min[c]
iii. 4 *N* HCl/dioxane, reflux, 3 h; it was stable to 10 *N* HCl/MeOH, 0–5°, 30 h[d]
iv. Me_3SiI/CCl_4 or $CHCl_3$, 25°, < 0.1 h, 100% yield[e]

[a] H. C. Beyerman and J. S. Bontekoe, *Proc. Chem. Soc.*, 249 (1961).
[b] H. C. Beyerman and G. J. Heiszwolf, *J. Chem. Soc.*, 755 (1963).
[c] F. M. Callahan, G. W. Anderson, R. Paul, and J. E. Zimmerman, *J. Am. Chem. Soc.*, **85**, 201 (1963).
[d] U. Eder, G. Haffer, G. Neef, G. Sauer, A. Seeger, and R. Wiechert, *Chem. Ber.*, **110**, 3161 (1977).
[e] M. E. Jung and M. A. Lyster, *J. Org. Chem.*, **42**, 3761 (1977).

23. Allyl Ether: $ROCH_2CH{=}CH_2$, 23

Allyl ethers are stable to moderately acidic conditions (1 *N* HCl, reflux, 10 h).[a]

Formation

$$ROH + CH_2{=}CHCH_2Br \xrightarrow[NaH,\ C_6H_6,\ 90\text{–}100\%^c]{NaOH,\ C_6H_6,\ reflux,\ 1.5\ h^b\ or} \mathbf{23}$$

Cleavage

$$(1)\quad \mathbf{23} \xrightarrow[100°,\ 15\ min]{KO\text{-}t\text{-}Bu/DMSO^d} ROCH{=}CHCH_3 \xrightarrow{i,\ ii,\ iii,\ or\ iv} ROH$$

i. 0.1 *N* HCl/acetone–H_2O, reflux, 30 min[d]
ii. $KMnO_4/NaOH$-H_2O, 10°, 100% yield. These basic conditions avoid acid-catalyzed acetonide cleavage.[a]
iii. $HgCl_2/HgO$, acetone–H_2O, 5 min, 100% yield[e]
iv. O_3[d]

$$(2)\quad \mathbf{23} \xrightarrow[reflux,\ 3\ h]{(Ph_3P)_3RhCl,\ DABCO,\ EtOH} \xrightarrow{Hg(II),\ pH\ 2} ROH,\ > 90\%^c$$

Allyl ethers are isomerized by $(Ph_3P)_3RhCl$, and KO-*t*-Bu/DMSO in the following order[f]:

$(Ph_3P)_3RhCl$: allyl > 2-methylallyl > but-2-enyl

KO-*t*-Bu: but-2-enyl > allyl > 2-methylallyl

(3) **23** $\xrightarrow[60\text{–}80°,\ 24\ h,\ 80\text{–}95\%]{Pd/C\text{–}H_2O,\ MeOH,\ cat.\ TsOH\ or\ HClO_4}$ ROH[g]

Benzyl ethers, nitriles, epoxides, esters, and α,β-unsaturated carbonyl compounds are stable to these cleavage conditions.[g]

(4) **23** $\xrightarrow[reflux,\ 1\ h,\ 50\%]{SeO_2/HOAc\text{–}dioxane[h]}$ $[ROCH(OH)CH{=}CH_2]\rightarrow$ ROH

[a] J. Cunningham, R. Gigg, and C. D. Warren, *Tetrahedron Lett.*, 1191 (1964).
[b] R. Gigg and C. D. Warren, *J. Chem. Soc. C*, 2367 (1969).
[c] E. J. Corey and W. J. Suggs, *J. Org. Chem.*, **38**, 3224 (1973).
[d] J. Gigg and R. Gigg, *J. Chem. Soc. C*, 82 (1966).
[e] R. Gigg and C. D. Warren, *J. Chem. Soc. C*, 1903 (1968).
[f] P. A. Gent and R. Gigg, *J. Chem. Soc., Chem. Commun.*, 277 (1974).
[g] R. Boss and R. Scheffold, *Angew. Chem., Inter. Ed. Engl.*, **15**, 558 (1976).
[h] K. Kariyone and H. Yazawa, *Tetrahedron Lett.*, 2885 (1970).

24. Cinnamyl Ether: $ROCH_2CH{=}CHC_6H_5$, 24

***Formation* (→) / *Cleavage* (←)[a]**

$$ROH \xrightarrow[50°,\ 5\ h]{PhCH{=}CHCH_2Br,\ HgCN,\ C_6H_6} \mathbf{24} \xrightarrow[H_2O]{H_2S,\ NaHCO_3} ROH$$

$$\mathbf{24} \xrightarrow[80\text{–}90\%]{-2.58\ V,\ Et_4N^+I^-} ROH$$

A cinnamyl ether is stable to acidic hydrolysis (10 *N* HCl, 20°, 20 h). Electrolytic treatment of an *N*-cinnamyl group would probably lead to reduction of the double bond, rather than to cleavage of the protective group, although a cinnamyl group can probably be removed electrolytically from RCOO-cinnamyl.[a]

[a] A. Ya. Veinberg, V. G. Mairanovskii, and G. I. Samokhavalov, *J. Gen. Chem. USSR*, **38**, 643 (1968).

25. *p*-Chlorophenyl Ether: ROC_6H_4-*p*-Cl, 25

***Formation* (→) / *Cleavage* (←)[a]**

$$ROH \xrightarrow{MeSO_2Cl,\ Py} \xrightarrow{p\text{-}ClC_6H_4ONa} \mathbf{25}$$

$$\mathbf{25} \xrightarrow{H_3O^+} \xrightarrow{Li/NH_3} ROH$$

A *p*-chlorophenyl ether was used in this synthesis to minimize ring sulfonation during cyclization of a diketo ester with conc H_2SO_4/HOAc.[a]

[a] J. A. Marshall and J. J. Partridge, *J. Am. Chem. Soc.*, **90**, 1090 (1968).

26. Benzyl Ether: $ROCH_2C_6H_5$, 26

Formation

Benzyl ethers were originally prepared under rather drastic conditions (e.g., ROH + $PhCH_2Cl$, powdered KOH, 130–140°, 86% yield).[a] Some more recent milder methods are as follows:

(1) ROH $\xrightarrow{NaH/THF}$ $\xrightarrow[20°,\ 3\ h]{PhCH_2Br,\ Bu_4N^+I^-[b]}$ $ROCH_2Ph$, 100%

This method was used to protect hindered hydroxyl groups in glucosides.[b]

(2) ROH + $PhCH_2Cl$ $\xrightarrow[20°,\ 1\text{–}3\ h,\ 85\text{–}95\%]{NaH,\ NaNH_2\ or\ NaOH/DMSO[c]}$ $ROCH_2Ph$

(3) ROH $\xrightarrow[25°]{PhCH_2X,\ Ag_2O/DMF}$ $\xrightarrow{H_3O^+}$ **26**, good yields[d]

X = Cl, Br

This method was used to avoid deacylation in the starting carbohydrate.[e]

(4) ROH $\xrightarrow[reflux,\ 3\ h,\ 80\text{–}90\%]{PhCH_2Cl,\ Ni(acac)_2[f]}$ $ROCH_2Ph$ + HCl ↑

Cleavage

In general benzyl ethers are cleaved by catalytic (eqs. 1 and 2) or chemical (eq. 3) reduction. Some other mild methods are also described.

(1) $ROCH_2Ph$ $\xrightarrow[95\%]{H_2/Pd\text{–}C,\ EtOH[g]}$ ROH + $PhCH_3$

Pd is used since Pt would hydrogenate the aromatic ring.[g]

An isolated double bond has been selectively reduced without cleaving a benzyl ether (H_2/5% Pd–C, 97% yield).[h]

(2) $ROCH_2Ph + Pd/C \xrightarrow[1\text{–}8\ h,\ 80\text{–}90\%]{cyclohexene^{i}} \text{or} \xrightarrow[25°,\ 2\ h,\ good\ yields]{cyclohexadiene^{j}} ROH$

Transfer hydrogenation may be used to remove benzyl ethers from S-containing peptides; *t*-butoxycarbonyl protective groups are stable. However benzyl esters, *N*-benzyloxycarbonyl, *N*-benzyl, and nitro groups are unstable to this method.[i,j]

(3) $ROCH_2Ph \xrightarrow{Na/NH_3{}^{k}\ or\ EtOH^{l}} ROH$

(4) Benzyl ethers can be cleaved by electrolytic reduction (-3.1 V, $R_4N^+F^-$, DMF).[m]

(5) $ROCH_2Ph \xrightarrow[25°,\ 15\ min,\ 100\%]{Me_3SiI,\ CH_2Cl_2{}^{n}} ROH$

(6) Benzyl ethers have been cleaved by lithium aluminum hydride (THF, reflux, 10 h → 25°, 12 h, 82% yield).[o]

(7) $ROCH_2Ph \xrightarrow[25°,\ 50\%]{CrO_3/HOAc^{p}} ROCOPh\ [\rightarrow ROH + HOOCPh]$

This method has been used to remove benzyl ethers from carbohydrates that contain functional groups sensitive to catalytic hydrogenation or dissolving metals. Esters are stable, but glycosides or acetals are cleaved.[p]

(8) Benzyl ethers have been cleaved by some other oxidants (e.g., $Ph_3C^+BF_4^-$, 25°, 0.5 h, 65% yield[q]; UF_6/FCl_2CClF_2, 44–69% yield[r]).

(9) Benzyl ethers are cleaved oxidatively by a cation radical under homogeneous electron transfer conditions:

$$ROCH_2Ph + [Ar_3N \xrightarrow[20°,\ CH_3CN,\ LiClO_4]{1.4\text{–}1.7\ V} Ar_3N^{\ddagger}] \xrightarrow[80\text{–}90\%]{Py\ or\ NaHCO_3} ROH^{s}$$

Ar = mono- or dibromophenyl

Benzyl or *p*-methoxybenzyl ethers can be selectively cleaved by arylamine cation radicals with different substituents.[s]

(10) Benzyl[t] and *p*-methoxybenzyl[t,u] ethers are cleaved by electrolytic oxidation (1.9 V, CH_3CN, $LiClO_4$, 60–70% yield).

(11) $ROCH_2Ph \xrightarrow[0°]{BBr_3/CCl_4{}^{v}} \text{or} \xrightarrow[20°,\ 2\text{–}24\ h,\ 85\text{–}90\%]{BF_3\cdot Et_2O,\ EtSH^{w}} ROH$

(12) $ROCH_2Ph \xrightarrow[0\text{–}25°]{Br_2/CCl_4,h\nu} \xrightarrow{aq\ Na_2CO_3} ROH,\ good\ yields^{x}$

Free radical bromination of the benzyl hydrogen followed by hydrolysis was used to remove the benzyl ether protective group from a carbohydrate with a functional group unstable to catalytic hydrogenation. This procedure could not be used selectively in the presence of trityl ethers or benzylidene acetals.[x]

[a] H. G. Fletcher, *Methods Carbohydr. Chem.*, **II**, 166 (1963).
[b] S. Czernecki, C. Georgoulis, and C. Provelenghiou, *Tetrahedron Lett.*, 3535 (1976).
[c] T. Iwashige and H. Saeki, *Chem. Pharm. Bull.*, **15**, 1803 (1967).
[d] R. Kuhn, I. Löw, and H. Trischmann, *Chem. Ber.*, **90**, 203 (1957).
[e] I. Croon and B. Lindberg, *Acta Chem. Scand.*, **13**, 593 (1959).
[f] M. Yamashita and Y. Takegami, *Synthesis*, 803 (1977).
[g] C. H. Heathcock and R. Ratcliffe, *J. Am. Chem. Soc.*, **93**, 1746 (1971).
[h] J. S. Bindra and A. Grodski, *J. Org. Chem.*, **43**, 3240 (1978).
[i] G. M. Anantharamaiah and K. M. Sivanandaiah, *J. Chem. Soc., Perkin Trans. 1*, 490 (1977).
[j] A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki, and J. Meienhofer, *J. Org. Chem.*, **43**, 4194 (1978).
[k] C. M. McCloskey, *Adv. Carbohydr. Chem.*, **12**, 137 (1957).
[l] E. J. Reist, V. J. Bartuska, and L. Goodman, *J. Org. Chem.*, **29**, 3725 (1964).
[m] V. G. Mairanovsky, *Angew. Chem., Inter. Ed. Engl.*, **15**, 281 (1976).
[n] M. E. Jung and M. A. Lyster, *J. Org. Chem.*, **42**, 3761 (1977).
[o] J. P. Kutney, N. Abdurahman, C. Gletsos, P. LeQuesne, E. Piers, and I. Vlattas, *J. Am. Chem. Soc.*, **92**, 1727 (1970).
[p] S. J. Angyal and K. James, *Carbohydr. Res.*, **12**, 147 (1970).
[q] D. H. R. Barton, P. D. Magnus, G. Smith, G. Streckert, and D. Zurr, *J. Chem. Soc., Perkin Trans. 1*, 542 (1972).
[r] G. A. Olah, J. Welch, and T.-L. Ho, *J. Am. Chem. Soc.*, **98**, 6717 (1976).
[s] W. Schmidt and E. Steckhan, *Angew. Chem., Inter. Ed. Engl.*, **18**, 801 (1979).
[t] E. A. Mayeda, L. L. Miller, and J. F. Wolf, *J. Am. Chem. Soc.*, **94**, 6812 (1972).
[u] S. M. Weinreb, G. A. Epling, R. Comi, and M. Reitano, *J. Org. Chem.*, **40**, 1356 (1975).
[v] J. P. Kutney, N. Abdurahman, P. LeQuesne, E. Piers, and I. Vlattas, *J. Am. Chem. Soc.*, **88**, 3656 (1966).
[w] K. Fuji, K. Ichikawa, M. Node, and E. Fujita, *J. Org. Chem.*, **44**, 1661 (1979).
[x] J. N. BeMiller, R. E. Wing, and C. Y. Meyers, *J. Org. Chem.*, **33**, 4292 (1968).

27. *p*-Methoxybenzyl Ether: $ROCH_2C_6H_4$-*p*-OCH_3, 27

The methods used to form and cleave benzyl ethers (compound **26**) should be consulted; the conditions described in **Cleavage** eqs. 9 and 10 have been used to cleave *p*-methoxybenzyl ethers.

28. *o*-Nitrobenzyl Ether: $ROCH_2C_6H_4$-*o*-NO_2, 28

29. *p*-Nitrobenzyl Ether: $ROCH_2C_6H_4$-*p*-NO_2, 29

Compounds **28** and **29** can be prepared and cleaved by many of the methods described for benzyl ethers (compound **26**). In addition, compound **28** can be cleaved by irradiation (320 nm, 10 min, quant yield of carbohydrate[a]; 280 nm, 95% yield of nucleotide[b]). Compound **29** has been cleaved by electrolytic reduction (−1.1 V, DMF, $R_4N^+X^-$, 60% yield).[c]

[a] U. Zehavi, B. Amit, and A. Patchornik, *J. Org. Chem.*, **37**, 2281 (1972); U. Zehavi and A. Patchornik, *J. Org. Chem.*, **37**, 2285 (1972).

[b] E. Ohtsuka, S. Tanaka, and M. Ikehara, *J. Am. Chem. Soc.*, **100**, 8210 (1978).

[c] V. G. Mairanovsky, *Angew. Chem., Inter. Ed. Engl.*, **15**, 281 (1976).

30. *p*-Halobenzyl Ether: $ROCH_2C_6H_4$-*p*-X, X = Br, Cl, 30

p-Halobenzyl ethers have been prepared to protect side chain hydroxyl groups in amino acids. They are stable to the conditions of acidic hydrolysis (50% CF_3CO_2H) used to remove amine protective groups; they are cleaved by HF (0°, 10 min).[a]

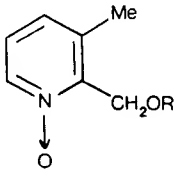
[a] D. Yamashiro, *J. Org. Chem.*, **42**, 523 (1977).

31. *p*-Cyanobenzyl Ether: $ROCH_2C_6H_4$-*p*-CN, 31

Compound **31**, prepared from an alcohol and the benzyl bromide in the presence of sodium hydride (74% yield), can be cleaved by electrolytic reduction (−2.1 V, 71% yield). It is stable to electrolytic removal (−1.4 V) of a tritylone ether [i.e., 9-(9-phenyl-10-oxo)anthryl ether].[a]

[a] C. van der Stouwe and H. J. Schäfer, *Tetrahedron Lett.*, 2643 (1979).

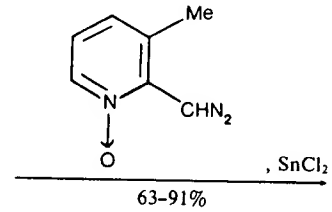
32. 3-Methyl-2-picolyl *N*-Oxido Ether:



, 32

The authors prepared a number of substituted 2-diazomethylene derivatives of picolyl oxide to use for monoprotection of the cis glycol system in nucleosides. The 3-methyl derivative proved most satisfactory.[a]

***Formation* (→) / *Cleavage* (←)[a]**



ROH **32**

aq HOAc, 70°, 3 h ← quant

ROH = ribonucleosides

[a] Y. Mizuno, T. Endo, and K. Ikeda, *J. Org. Chem.*, **40**, 1385 (1975); Y. Mizuno, T. Endo, and T. Nakamura, *J. Org. Chem.*, **40**, 1391 (1975).

33. Diphenylmethyl Ether: $ROCH(C_6H_5)_2$, 33

See also the methods used to prepare and cleave benzyl ethers (compound **26**).

Formation

(1) $ROH \xrightarrow[\text{reflux, 4–9 h, 65–92\%}]{(Ph_2CHO)_3PO,\ \text{cat. } CF_3COOH,\ CH_2Cl_2{}^a} ROCHPh_2$

R = *n*-Pr, *i*-Pr, *n*-Bu, $PhCH_2$, Ph_2CH

(2) $ROH \xrightarrow[\text{12 h, 70\%}]{Ph_2CHOH,\ \text{concd } H_2SO_4{}^b} ROCHPh_2$

R = Me

Cleavage

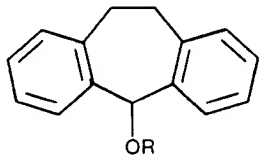
(1) $ROCHPh_2 \xrightarrow[\text{reflux, 24 h, 91\%}]{\text{Pd–C/AlCl}_3,\ \text{cyclohexene}^c} ROH$

(2) $ROCHPh_2 \xrightarrow{-3.0\ \text{V, DMF, } R_4N^+X^-{}^b} ROH$

[a] L. Lapatsanis, *Tetrahedron Lett.*, 3943 (1978).

[b] V. G. Mairanovsky, *Angew. Chem., Inter. Ed. Engl.*, **15**, 281 (1976).

[c] G. A. Olah, G. K. S. Prakash, and S. C. Narang, *Synthesis*, 825 (1978).

34. 5-Dibenzosuberyl Ether:  , 34

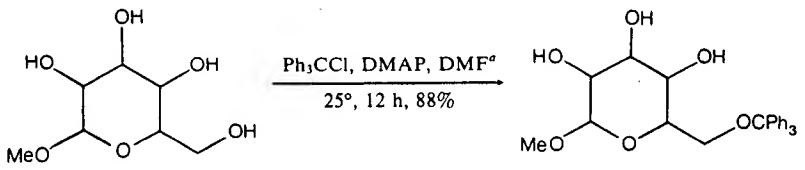
Compound **34** is prepared from an alcohol and the suberyl chloride (which has also been used to protect amines, thiols, and carboxylic acids) in the presence of triethylamine (CH_2Cl_2, 20°, 3 h, 75% yield). It is cleaved by acidic hydrolysis (1 *N* HCl/dioxane, 20°, 6 h, 80% yield).[a]

[a] J. Pless, *Helv. Chim. Acta*, **59**, 499 (1976).

35. Triphenylmethyl Ether: $ROC(C_6H_5)_3$, 35

The bulky triphenylmethyl group has been used to protect, selectively, the primary hydroxyl groups in carbohydrates and nucleosides.

Formation

(1) 

DMAP = 4-*N*,*N*-dimethylaminopyridine

A secondary alcohol reacts more slowly (40–45°, 18–24 h, 68–70% yield).[a]

(2) $ROH + C_5H_5N^+CPh_3BF_4^- \xrightarrow[60\text{–}70°,\ 75\text{–}90\%]{CH_3CN,\ Py^b} ROCPh_3$

Triphenylmethyl ethers can be prepared more readily with triphenylmethylpyridinium fluoroborate than with triphenylmethyl chloride/pyridine.[b]

(3) $ROH + ClCPh_2C_6H_4\text{-}p\text{-}(P) \xrightarrow[5\text{ days, }90\%]{Py,\ 25^{oc}} ROCPh_2C_6H_4\text{-}p\text{-}(P)$

(P) = styrene-divinylbenzene polymer

Triarylmethyl ethers of primary hydroxyl groups in gluocopyranosides have been prepared using a polymeric form of triphenylmethyl chloride. Although the yields are not improved, workup is simplified.[c]

Cleavage

Triphenylmethyl ethers have been cleaved by a number of methods, including aqueous or anhydrous acidic hydrolysis, and catalytic, chemical, or electrolytic reduction.

(1) $ROCPh_3 \xrightarrow[96\%]{HOAc,\ 56°,\ 7.5\ h^d} ROH$

ROH = C_3-Δ^6-hydroxy steroid

(2) $ROCPh_3 \xrightarrow[20°,\ 2\text{–}30\ min]{90\%\ CF_3COOH,\ t\text{-}BuOH} \xrightarrow[resin]{Bio\text{-}Rad\ 1\times 2\ (OH^-)} ROH^e,\ 67\text{–}100\%$

ROH = 5′-OH of a nucleoside. Bio-Rad resin neutralizes the acidic hydrolysis reaction and minimizes cleavage of glycosyl bonds.[e]

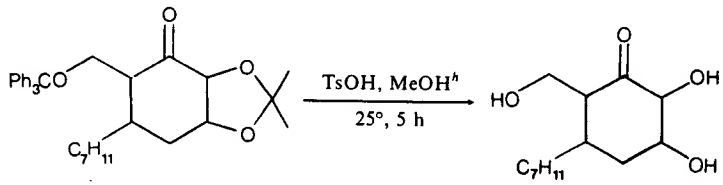
(3) $ROCPh_3 \xrightarrow[25°,\ 16\ h,\ 81\%]{SiO_2,\ C_6H_6^f} ROH$

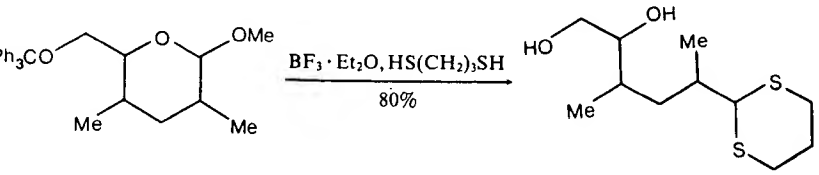
ROH = carbohydrate

This cleavage reaction is carried out on a column.[f]

(4) $ROCPh_3 \xrightarrow[0°,\ 1\ h,\ 91\%]{HCl(g),\ CHCl_3^g} ROH$

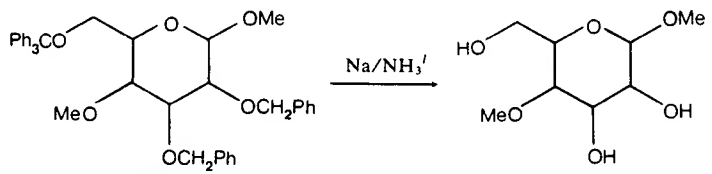
ROH = carbohydrate

(5) 

(6) 

(7) $ROCPh_3 \xrightarrow[20°,\ 14\ h,\ 80\%]{H_2/Pd,\ EtOH^{j,k}} ROH$

(8)



(9) $ROCPh_3 \xrightarrow{-2.9\ V,\ R_4N^+X^-,\ DMF[m]} ROH$

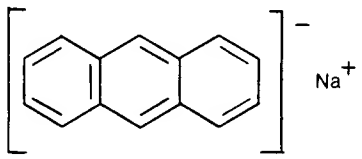
(10) $CH_3CH(OCPh_3)(CH_2)_4CH_2OCPh_3 \xrightarrow[20°,\ 15\ min,\ 91\%]{Ph_3C^+BF_4^-,CH_2Cl_2[n]} CH_3CO(CH_2)_4CH_2OH$

Since a secondary alcohol is oxidized in preference to a primary alcohol by triphenylmethyl tetrafluoroborate, this reaction results in selective protection of a primary alcohol.[n]

[a] S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 95 (1979).
[b] S. Hanessian and A. P. A. Staub, *Tetrahedron Lett.*, 3555 (1973).
[c] J. M. J. Fréchet and K. E. Haque, *Tetrahedron Lett.*, 3055 (1975).
[d] R. T. Blickenstaff, *J. Am. Chem. Soc.*, **82**, 3673 (1960).
[e] M. MacCoss and D. J. Cameron, *Carbohydr. Res.*, **60**, 206 (1978).
[f] J. Lehrfeld, *J. Org. Chem.*, **32**, 2544 (1967).
[g] Y. M. Choy and A. M. Unrau, *Carbohydr. Res.*, **17**, 439 (1971).
[h] A. Ichihara, M. Ubukata, and S. Sakamura, *Tetrahedron Lett.*, 3473 (1977).
[i] P.-E. Sum and L. Weiler, *Can. J. Chem.*, **56**, 2700 (1978).
[j] R. N. Mirrington and K. J. Schmalzl, *J. Org. Chem.*, **37**, 2877 (1972).
[k] S. Hanessian and G. Rancourt, *Pure Appl. Chem.*, **49**, 1201 (1977).
[l] P. Kováč and Š. Bauer, *Tetrahedron Lett.*, 2349 (1972).
[m] V. G. Mairanovsky, *Angew. Chem., Inter. Ed. Engl.*, **15**, 281 (1976).
[n] M. E. Jung and L. M. Speltz, *J. Am. Chem. Soc.*, **98**, 7882 (1976).

36. α-Naphthyldiphenylmethyl Ether: $ROC(C_6H_5)_2$-α-$C_{10}H_7$, 36

Compound **36** has been prepared to protect, selectively, the 5′-OH group in nucleosides. It is prepared from α-naphthyldiphenylmethyl chloride in pyridine (65% yield), and cleaved selectively in the presence of a *p*-methoxyphenyldiphenylmethyl ether with sodium anthracenide, **a**, (THF, 97% yield).[a]



a

[a] R. L. Letsinger and J. L. Finnan, *J. Am. Chem. Soc.*, **97**, 7197 (1975).

37. *p*-Methoxyphenyldiphenylmethyl Ether: $ROC(C_6H_5)_2C_6H_4$-*p*-OCH_3, 37

In his work with nucleosides and nucleotides, Khorana[a,b] required a protective group that would be selective for primary hydroxyl groups. However, it had to be more easily cleaved by acid hydrolysis than the triphenylmethyl ether, since acid cleavage of the latter group also cleaved glycosyl bonds. Introduction of *p*-methoxy groups increased the rate of hydrolysis by about one order of magnitude for each *p*-methoxy substituent. For 5′-protected uridine derivatives in 80% HOAc, 20°, the time for hydrolysis was as follows:

$ROC(C_6H_5)_m(C_6H_4$-*p*-$OMe)_n$

n = 0, m = 3, 48 h

n = 1, m = 2, 2 h (therefore the most useful compound)

n = 2, m = 1, 15 min

n = 3, m = 0, 1 min

Cleavage

Compound **37** is cleaved by sodium naphthalenide in HMPA (90% yield).[c] It is not cleaved by sodium anthracenide, used to cleave α-naphthyldiphenylmethyl ethers.[d]

[a] H. G. Khorana, *Pure Appl. Chem.*, **17**, 349 (1968).
[b] M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, *J. Am. Chem. Soc.*, **84**, 430 (1962).
[c] G. L. Greene and R. L. Letsinger, *Tetrahedron Lett.*, 2081 (1975).
[d] R. L. Letsinger and J. L. Finnan, *J. Am. Chem. Soc.*, **97**, 7197 (1975).

38. *p*-(*p*′-Bromophenacyloxy)phenyldiphenylmethyl Ether: $ROC(C_6H_5)_2C_6H_4$-*p*-$OCH_2COC_6H_4$-*p*-Br, 38

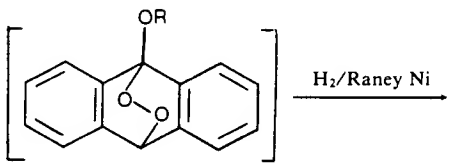
Several substituted triphenylmethyl ethers were developed to provide selective protection for the 5′-OH group in nucleosides. Compound **38** proved the most satisfactory. It is prepared from the corresponding triarylmethyl chloride, and cleaved by reductive cleavage (Zn/HOAc) of the phenacyl ether to the *p*-hydroxyphenyldiphenylmethyl ether followed by acidic hydrolysis with HCOOH.[a]

[a] A. T.-Rigby, Y.-H. Kim, C. J. Crosscup, and N. A. Starkovsky, *J. Org. Chem.*, **37**, 956 (1972).

39. 9-Anthryl Ether: RO-9-anthryl, 39

Compound **39**, formed by reaction of the anion of 9-hydroxyanthracene and an *O*-tosylate, can be cleaved by oxidation with singlet oxygen, a new way to remove a protective group.

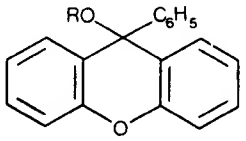
Cleavage[a]

39 $\xrightarrow[-30°]{(PhO)_3P,\ O_3}$  $\xrightarrow{H_2/Raney\ Ni}$

ROH + 9-hydroxyanthrone

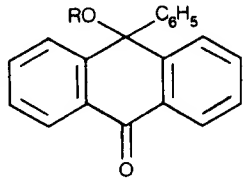
quant

[a] W. E. Barnett and L. L. Needham, *J. Chem. Soc., Chem. Commun.*, 1383 (1970); *J. Org. Chem.*, **36**, 4134 (1971).

40. 9-(9-Phenyl)xanthenyl Ether:  **, 40**

Compound **40** has been prepared, from the xanthenyl chloride, 68–87% yield, to protect 5′-OH groups in nucleosides; it is readily cleaved by acidic hydrolysis (80% HOAc, 20°, 8–15 min, 100% yield). Compound **40** forms better crystalline derivatives than the corresponding di(*p*-methoxyphenyl)phenylmethyl ether, which is cleaved in 16 minutes under similar conditions.[a]

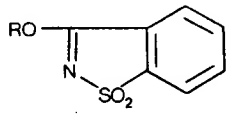
[a] J. B. Chattopadhyaya and C. B. Reese, *J. Chem. Soc., Chem. Commun.*, 639 (1978).

41. 9-(9-Phenyl-10-oxo)anthryl Ether (Tritylone Ether):  **, 41**

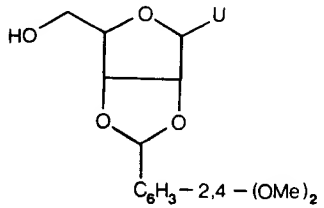
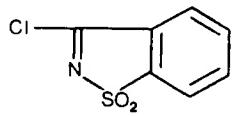
Compound **41** has been prepared to protect primary hydroxyl groups in the presence of secondary hydroxyl groups, by reaction of an alcohol with 9-phenyl-9-hydroxyanthrone (cat. TsOH, C_6H_6, reflux, 55–95% yield).[a,b] It can be cleaved under the harsh conditions of Wolff-Kishner reduction (H_2NNH_2, NaOH, 200°, 88% yield),[a] and by electrolytic reduction (−1.4 V, LiBr, MeOH, 80–85% yield).[b] It is stable to acidic hydrolysis (10% HCl, 54 h).[a]

[a] W. E. Barnett, L. L. Needham, and R. W. Powell, *Tetrahedron*, **28**, 419 (1972).

[b] C. van der Stouwe and H. J. Schäfer, *Tetrahedron Lett.*, 2643 (1979).

42. Benzisothiazolyl *S,S*-Dioxido Ether:  **, 42**

Formation (→) / *Cleavage* (←)[a]

 + 

$\xrightarrow[-18°,\ 10\ h,\ 70\%]{Py,\ mol\ sieves}$

$\xleftarrow[20°,\ 15\ h]{concd\ NH_3,\ Py}$

42a

Note that compound **42** is an imino ether that can be cleaved under basic conditions.

[a] H. Sommer and F. Cramer, *Chem. Ber.*, **107**, 24 (1974).

Silyl Ethers

An active hydrogen can be protected as a silyl derivative; the order of reactivity is reported[a] as ROH > ArOH > COOH > NH > CONH > SH. Reaction of a perfluorinated resin of trimethylsilyl trifluoromethanesulfonate with a variety of functional groups to form trimethylsilyl derivatives indicates a different order of reactivity[b]: EtSH, 29°, Et_3N, 2 h, 91% yield > CH_3COOH, 25°, Et_3N, 3 h, 54% yield > Et_2NH, 28°, 6 h, 94% yield > EtOH, 29°, 12 h, 100% yield > PhOH, 23°, Et_3N, 18 h, 86% yield.

A series of silyl groups (e.g., methyldiisopropyl-, tetramethyleneisopropyl-, *t*-butyldimethyl-, triisopropyl-, and tetramethylene-*t*-butyl-) was prepared to study selective protection of 2′-, 3′-, and 5′-hydroxyl groups in ribonucleosides.[c] The *t*-butyldimethylsilyl ether proves to be one of the most useful silyl derivatives for a wide range of alcohols.[d]

Trimethylsilyl ethers of primary hydroxyl groups are readily hydrolyzed (K_2CO_3, or HOAc/MeOH, 0°); the rate constant for hydrolysis of a trimethylsilyl ether of a secondary hydroxyl group is smaller by a factor of 25.[e] The order of hydrolysis of some other trimethylsilyl (TMS) derivatives is as follows[a]: > NTMS > -COOTMS > ArOTMS > ROTMS; -STMS > -OTMS.

[a] B. E. Cooper, *Chem. Ind. (London)*, 794 (1978).

[b] S. Murata and R. Noyori, *Tetrahedron Lett.*, **21**, 767 (1980).

[c] K. K. Ogilvie, E. A. Thompson, M. A. Quilliam, and J. B. Westmore, *Tetrahedron Lett.*, 2865 (1974).

[d] For a discussion of the use of this ether in nucleoside syntheses, see K. K. Ogilvie, S. L. Beaucage, A. L. Schifman, N. Y. Theriault, and K. L. Sadana, *Can. J. Chem.*, **56**, 2768 (1978).

[e] A. G. McInnes, *Can. J. Chem.*, **43**, 1998 (1965).

43. Trimethylsilyl Ether (TMS Ether): $ROSi(CH_3)_3$, 43

Many reagents (e.g., trimethylchlorosilane, hexamethyldisilazane, *N,O*-bistrimethylsilylacetamide, bistrimethylsilylurea, *N*-trimethylsilyl-*N,N'*-diphenylurea, trimethylsilylimidazole, trimethylsilyldiethylamine, and monotrimethylsilylacetamide) form trimethylsilyl derivatives of compounds with an active hydrogen.[a,b] Some conditions that have been used to prepare trimethylsilyl ethers are shown below.

Formation

(1) $ROH + Me_3SiCl \xrightarrow[25°,\ 8\ h,\ 90\%]{Et_3N,\ THF^c} ROSiMe_3$

(2) $ROH + Me_3SiCl \xrightarrow[25°,\ 12\ h,\ 75\text{–}95\%]{Li_2S,\ CH_3CN^d} ROSiMe_3$

Silylation occurs under neutral conditions with this combination of reagents.[d]

(3) $ROH + (Me_3Si)_2NH \xrightarrow[20°,\ 5\ min,\ \sim 100\%]{Me_3SiCl,\ Py^e} ROSiMe_3$

ROH = carbohydrate

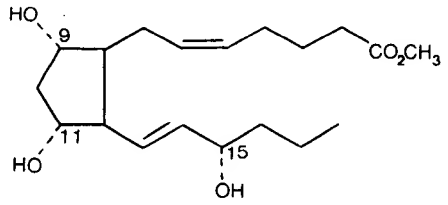
(4) $ROH + (Me_3Si)_2O \xrightarrow[reflux,\ 4\ days,\ 80\text{–}90\%]{C_5H_5\overset{+}{N}H\ OTs^-,\ C_6H_6,\ mol\ sieves^f} ROSiMe_3$

These are only mildly acidic conditions, suitable for acid-sensitive alcohols.[f]

(5) $ROH + Me_3SiNEt_2$[g] $\rightarrow ROSiMe_3$

Trimethylsilyldiethylamine selectively silylates equatorial hydroxyl groups in quantitative yield (4–10 h, 25°). The report indicated no reaction at axial hydroxyl groups.[g]

In the prostaglandin series the order of reactivity of trimethylsilyldiethylamine is $C_{11} > C_{15} >> C_9$ (no reaction). These trimethylsilyl ethers of secondary hydroxyl groups were hydrolyzed with aqueous methanol containing a trace of acetic acid.[h]



(6) $ROH + CH_3C(OSiMe_3)=NSiMe_3 \xrightarrow[78°]{DMF^i} ROSiMe_3$

ROH = C_{14}-hydroxy steroid

N,O-Bis(trimethylsilyl)acetamide was used to protect a sterically hindered, tertiary hydroxyl group. The resulting trimethylsilyl ether, stable to a Grignard reaction, was slowly cleaved with 0.1 *N* HCl/10% aq THF, 25°.[i]

(7) $ROH + Me_3SiCH_2CO_2Et \xrightarrow[25°,\ 1\text{–}3\ h,\ 90\%]{cat.\ n\text{-}Bu_4N^+F^-[j]} ROSiMe_3$

Use of ethyl trimethylsilylacetate/tetra-*n*-butylammonium fluoride allows isolation of pure products under nonaqueous conditions. This reagent also converts aldehydes and ketones to trimethylsilyl enol ethers.[j]

(8) $ROH + Me_3SiNHCO_2SiMe_3 \xrightarrow[rapid,\ 80\text{–}95\%]{THF^k} ROSiMe_3$

This reagent also silylates phenols and carboxyl groups.[k]

(9) $ROH + Me_3SiNHSO_2OSiMe_3 \xrightarrow[30°,\ 0.5\ h,\ 92\text{–}98\%]{CH_2Cl_2[l]} ROSiMe_3$

Higher yields of trimethylsilyl derivatives are realized by reaction of aliphatic, aromatic, and carboxylic hydroxyl groups with *N,O*-bis(trimethylsilyl) sulfamate than by reaction with *N,O*-bis(trimethylsilyl)acetamide.[l]

(10) $ROH + MeCH=C(OMe)OSiMe_3 \xrightarrow[50°,\ 30\text{–}50\ min,\ 83\text{–}99\%]{CH_3CN\ or\ CH_2Cl_2[m]} ROSiMe_3$

This reagent also silylates phenols, thiols, amides, and carboxyl groups.[m]

(11) $ROH + Me_3SiCH_2CH=CH_2 \xrightarrow[70\text{–}80°,\ 1\text{–}2\ h]{TsOH/CH_3CN[n]} ROSiMe_3,\ 90\text{–}95\%$

Formation of silyl derivatives may be effected by reaction with an allylsilane under acid catalysis. This silylating reagent is stable to moisture [Me_3SiCl and

$(Me_3Si)_2NH$ are readily hydrolyzed]. Allylsilanes can be used to protect alcohols, phenols, and carboxylic acids; there is no reaction with thiophenol. The method is also applicable to the formation of *t*-butyldimethylsilyl derivatives; the silyl ether of cyclohexanol was prepared in 95% yield from allyl-*t*-butyldimethylsilane.[n]

Cleavage

(1) $ROSiMe_3 \xrightarrow[\text{aprotic conditions}]{n\text{-}Bu_4N^+F^-,\ THF^c} ROH$

(2) $ROSiMe_3 \xrightarrow[0°,\ 45\ min,\ 100\%]{K_2CO_3,\ \text{anhyd MeOH}^o} ROH$

ROH = a carbohydrate

(3) $ROSiMe_3 \xrightarrow[20°,\ 10\ min,\ 100\%]{\text{citric acid/MeOH}^p} ROH$

ROH = 9-hydroxy prostaglandin derivative

Like other ethers with an α-hydrogen, trimethylsilyl ethers are oxidized by NBS/*hν* or Br_2[q]:

$$RCH_2OSiMe_3 + NBS/h\nu \xrightarrow{0°,\ 5\ h} RCO_2R,\ 80\%$$

$$C_6H_5CH_2OSiMe_3 + NBS/h\nu \xrightarrow{-20°,\ 2.5\ h} C_6H_5CHO,\ 48\%$$

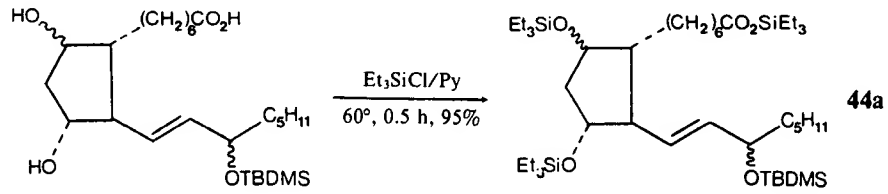
$$RR'CHOSiMe_3 + NBS/h\nu \xrightarrow[Py]{20°,\ 3.5\ h} RR'C{=}O,\ 55\text{–}75\%$$

[a] B. E. Cooper, *Chem. Ind. (London)*, 794 (1978).
[b] A. E. Pierce, *Silylation of Organic Compounds*, Pierce Chem. Co., Rockford, Illinois, 1968.
[c] E. J. Corey and B. B. Snider, *J. Am. Chem. Soc.*, **94**, 2549 (1972).
[d] G. A. Olah, B. G. B. Gupta, S. C. Narang, and R. Malhotra, *J. Org. Chem.*, **44**, 4272 (1979).
[e] C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Am. Chem. Soc.*, **85**, 2497 (1963).
[f] H. W. Pinnick, B. S. Bal, and N. H. Lajis, *Tetrahedron Lett.*, 4261 (1978).
[g] I. Weisz, K. Felföldi, and K. Kovács, *Acta Chim. Acad. Sci. Hung.*, **58**, 189 (1968).
[h] E. W. Yankee, U. Axen, and G. L. Bundy, *J. Am. Chem. Soc.*, **96**, 5865 (1974); E. L. Cooper and E. W. Yankee, *J. Am. Chem. Soc.*, **96**, 5876 (1974).
[i] M. N. Galbraith, D. H. S. Horn, E. J. Middleton, and R. J. Hackney, *J. Chem. Soc., Chem. Commun.*, 466 (1968).
[j] E. Nakamura, T. Murofushi, M. Shimizu, and I. Kuwajima, *J. Am. Chem. Soc.*, **98**, 2346 (1976).
[k] L. Birkofer and P. Sommer, *J. Organomet. Chem.*, **99**, C1 (1975).

[l] B. E. Cooper and S. Westall, *J. Organomet. Chem.*, **118**, 135 (1976).
[m] Y. Kita, J. Haruta, J. Segawa, and Y. Tamura, *Tetrahedron Lett.*, 4311 (1979).
[n] T. Morita, Y. Okamoto, and H. Sakurai, *Tetrahedron Lett.*, **21**, 835 (1980).
[o] D. T. Hurst and A. G. McInnes, *Can. J. Chem.*, **43**, 2004 (1965).
[p] G. L. Bundy and D. C. Peterson, *Tetrahedron Lett.*, 41 (1978).
[q] H. W. Pinnick and N. H. Lajis, *J. Org. Chem.*, **43**, 371 (1978).

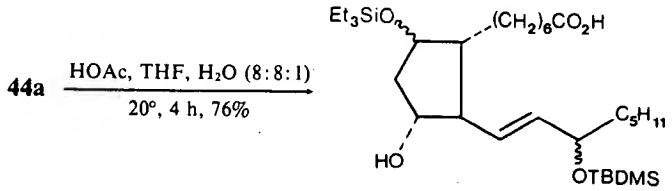
44. Triethylsilyl Ether: $ROSi(C_2H_5)_3$, 44

Formation[a]



44a

Cleavage[a]



TBDMS = *t*-butyldimethylsilyl (compound **46**).

More acidic conditions [HOAc, THF, H_2O (6:1:3), 45°, 3 h] cleave all of the protective groups (76% yield).[a]

[a] T. W. Hart, D. A. Metcalfe, and F. Scheinmann, *J. Chem. Soc., Chem. Commun.*, 156 (1979).

45. Isopropyldimethylsilyl Ether: $ROSi(CH_3)_2$-*i*-C_3H_7, 45

Formation (→) / *Cleavage* (←)[a]

$$ROH \underset{\text{35°, 10 min, 100\%}}{\overset{\text{25°, 48 h, 98\%}}{\rightleftarrows}} \mathbf{45}$$

$\text{HN(SiMe}_2\text{-}i\text{-Pr)}_2/\text{ClSiMe}_2\text{-}i\text{-Pr}$ (→); $\text{HOAc/H}_2\text{O (3:1)}$ (←)

ROH = PGE_2

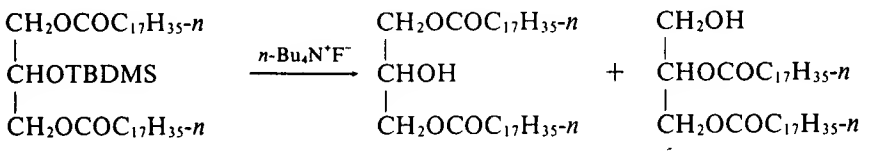
An isopropyldimethylsilyl ether is more easily cleaved than a tetrahydropyranyl ether. It is *not* stable to Grignard or Wittig reactions, or to Jones oxidation.[a]

[a] E. J. Corey and R. K. Varma, *J. Am. Chem. Soc.*, **93**, 7319 (1971).

46. *t*-Butyldimethylsilyl Ether (TBDMS Ether): $ROSi(CH_3)_2$-*t*-C_4H_9, 46

The *t*-butyldimethylsilyl group is one of the most useful silyl protective groups; a TBDMS ether is more stable to hydrolysis than a trimethylsilyl or dimethylisopropylsilyl ether, but is still readily cleaved by a variety of selective conditions. TBDMS and tetrahydropyranyl (THP) ethers are cleaved by mild acidic hydrolysis [HOAc-H_2O-THF (3:1:1), 25°] under similar conditions: THP: 4 h, 90% yield; TBDMS: 6 h, 96% yield. TBDMS esters are cleaved 20 times faster than TBDMS ethers by these conditions. In the course of prostaglandin synthetic studies, the TBDMS group was developed as a hydroxyl protective group that could be selectively removed in the presence of an acetate ester, a benzyl ether, a 2,2,2-trichloroethyl ether, or a tetrahydropyranyl ether. It is stable to the Wittig reaction, to Zn/MeOH, H_2/Pd-C, Na/NH_3, $(Me_2CHCH_2)_2AlH$, CrO_3/Py, H_2O_2/OH^-, and MeI/Ag_2O.[a]

During fluoride cleavage of a *t*-butyldimethylsilyl ether (protecting one hydroxyl group in a glycerol) an acyl group (protecting a second hydroxyl group) underwent migration[b]:



Examples of migration have been reported in other substrates (e.g., carbohydrates,[c] prostaglandins,[d] and nucleosides[e,f]). Consequently the *t*-butyldimethylsilyl group should not be used for hydroxyl protection when acyl migration is possible.

Formation

(1) $ROH + ClSiMe_2$-*t*-$Bu \xrightarrow[25°,\ 10\ h,\ high\ yields]{imidazole,\ DMF^a} ROTBDMS$

(2) $ROH + t\text{-}Bu\text{-}Me_2SiOClO_3 \xrightarrow[20\ min,\ 100\%]{CH_3CN,\ Py^g} ROTBDMS$

ROH = tertiary alcohols

In this example the yields with *t*-butyldimethylchlorosilane were unsatisfactory (10% yield, 72 h).[g]

(3) $ROH + ClSiMe_2$-*t*-$Bu \xrightarrow[25°,\ 5\text{–}8\ h,\ 75\text{–}95\%]{Li_2S,\ CH_3CN^h} ROTBDMS$

This reaction occurs under nearly neutral conditions.[h]

(4) $PhCH(OH)CH_2OH \xrightarrow[25°,\ 12\ h]{ClSiMe_2\text{-}t\text{-}Bu,\ DMAP,\ Et_3N,\ DMF^i}$

$PhCH(OH)CH_2OTBDMS + PhCH(OTBDMS)CH_2OH + PhCH(OTBDMS)CH_2OTBDMS$

60–90% minor products

(5) $c\text{-}C_6H_{11}OH + CH_2{=}CHCH_2SiMe_2\text{-}t\text{-}Bu \xrightarrow[70\text{–}80°,\ 2.5\ h]{TsOH/CH_3CN^j} ROTBDMS,\ 95\%$

See p. 41–42 for a discussion of allylsilanes.[j]

Cleavage

(1) $ROTBDMS \xrightarrow[25°,\ 30\ min,\ 100\%]{n\text{-}Bu_4N^+F^-,\ THF^a} ROH$

(2) $ROTBDMS \xrightarrow[25°,\ 4\ h,\ 95\%]{n\text{-}Bu_4N^+Cl^-/KF\cdot 2H_2O,\ CH_3CN^k} ROH$

This method readily generates fluoride ion *in situ*, and is reported to be suitable for reactions that normally require anhydrous conditions.[k]

(3) $ROTBDMS \xrightarrow[20°,\ 1\text{–}3\ h,\ 90\text{–}100\%]{aq\ HF,\ CH_3CN^l} ROH$

A solution of CH_3CN: 40% aq HF (95:5) efficiently hydrolyzes *t*-butyldimethylsilyl ethers under mild conditions.[l]

(4) $ROTBDMS \xrightarrow[25\text{–}80°,\ 15\ min\ to\ 5\ h]{HOAc\text{-}H_2O^a} ROH,\ high\ yield$

(5) $ROTBDMS \xrightarrow[20°,\ MeOH]{Dowex\ 50W\text{-}X8^m} ROH$

Dowex 50W-X8 is a carboxylic acid resin, H^+ form.

(6) $ROTBDMS \xrightarrow[0\text{–}25°,\ 15\ min\ to\ 3\ h,\ 70\text{–}90\%]{BF_3\cdot Et_2O,\ CHCl_3^n} ROH$

(7) ROTBDMS $\xrightarrow[0°,\ 15\ min,\ 92\%]{FeCl_3,\ Ac_2O^{o}}$ ROAc

ROH = 2-octanol. Methyl and benzyl ethers are also cleaved.[o]

(8) ROTBDMS $\xrightarrow[25°,\ 60\ h,\ 40\text{–}80\%]{Ph_3C^+BF_4^-\ or\ LiBF_4,\ CH_2Cl_2{}^{p}}$ ROH

ROH = primary or secondary alcohol

(9) 

→ thymidine

46a

Compound **46a** was subjected to the following conditions[e,q]:

i. 0.5 *N* NaOH/EtOH–H_2O, 22°, 24 h, 80% yield of thymidine.
ii. 15% NH_4OH/EtOH, 22°, 1.5 h (used to cleave -OAc), -OTBDMS stable.
iii. 9 *M* NH_4OH, 60°, 1 h (used to cleave -OAc), 6% yield of thymidine.
iv. H_2NNH_2/HOAc–Py, 22°, 24 h (used to cleave -NAc), -OTBDMS stable.
v. 80% HOAc, 90°, 15 min, 100% yield of thymidine.
vi. *n*-$Bu_4N^+F^-$/THF, 22°, 30 min, 100% yield of thymidine.

[a] E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
[b] G. H. Dodd, B. T. Golding, and P. V. Ioannou, *J. Chem. Soc., Chem. Commun.*, 249 (1975).
[c] F. Franke and R. D. Guthrie, *Aust. J. Chem.*, **31**, 1285 (1978).
[d] Y. Torisawa, M. Shibasaki, and S. Ikegami, *Tetrahedron Lett.*, 1865 (1979).
[e] K. K. Ogilvie, S. L. Beaucage, A. L. Schifman, N. Y. Theriault, and K. L. Sadana, *Can. J. Chem.*, **56**, 2768 (1978).
[f] S. S. Jones and C. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, 2762 (1979).
[g] T. J. Barton and C. R. Tully, *J. Org. Chem.*, **43**, 3649 (1978).
[h] G. A. Olah, B. G. B. Gupta, S. C. Narang, and R. Malhotra, *J. Org. Chem.*, **44**, 4272 (1979).
[i] S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 99 (1979).
[j] T. Morita, Y. Okamoto, and H. Sakurai, *Tetrahedron Lett.*, **21**, 835 (1980).
[k] L. A. Carpino and A. C. Sau, *J. Chem. Soc., Chem. Commun.*, 514 (1979).
[l] R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly, and S. M. Roberts, *Tetrahedron Lett.*, 3981 (1979).
[m] E. J. Corey, J. W. Ponder, and P. Ulrich, *Tetrahedron Lett.*, **21**, 137 (1980).
[n] D. R. Kelly, S. M. Roberts, and R. F. Newton, *Synth. Commun.*, **9**, 295 (1979).
[o] B. Ganem and V. R. Small, Jr., *J. Org. Chem.*, **39**, 3728 (1974).
[p] B. W. Metcalf, J. P. Burkhart, and K. Jund, *Tetrahedron Lett.*, **21**, 35 (1980).
[q] K. K. Ogilvie and D. J. Iwacha, *Tetrahedron Lett.*, 317 (1973).

47. (Triphenylmethyl)dimethylsilyl Ether: $ROSi(CH_3)_2C(C_6H_5)_3$, 47

Formation[a]

ROH + $BrSi(Me)_2CPh_3$ $\xrightarrow[20°,\ 80\text{–}90\%]{AgNO_3/DMF}$ or $\xrightarrow[100°,\ 12\ h,\ 50\text{–}75\%]{DMF}$ **47**

Cleavage[a]

(1) **47** $\xrightarrow{K_2CO_3/MeOH}$ ROH

(2) **47** $\xrightarrow{n\text{-}Bu_4N^+F^-/dioxane}$ ROH

(3) **47** $\xrightarrow{acidic\ hydrolysis}$ ROH

Acidic hydrolysis = 0.01 *M* H_2SO_4 or 0.01 *M* HCl/THF–H_2O (3:2), 20°, $t_{1/2}$ = 4 days; 0.2 *M* H_2SO_4/MeOH–THF (2:3), reflux, $t_{1/2}$ = 3 days; $TsOH \cdot H_2O/C_6H_6$, reflux, 15 h, 100% yield; CF_3CO_2H, 20°, 3 h, 100% yield.

Compound **47** is more stable to hydrolysis than is a *t*-butyldimethylsilyl ether. For example, it is stable to the following conditions: HOAc/Et_2O (1:1), 20°, 96 h; HOAc–H_2O–THF (6:4:1), reflux, 24 h; $TsOH/C_6H_6$, reflux, 20 h; 0.2 *M* H_2SO_4/MeOH–Et_2O (2:1), 20°, 92 h; NH_3/MeOH, 20°, 24 h. It is stable in an ether solution that is washed with 0.1 *M* NaOH.[a]

[a] D. J. Ager and I. Fleming, *J. Chem. Res., Synop.*, 6 (1977).

48. *t*-Butyldiphenylsilyl Ether: $ROSi(C_6H_5)_2$-*t*-C_4H_9, 48

Compound **48** was prepared to protect a primary hydroxyl group during a synthesis of thromboxane B_2 from D-glucose.[a]

Formation[a]

ROH + $ClSiPh_2$-*t*-Bu $\xrightarrow[25\text{–}60°,\ 75\text{–}87\%]{imidazole,\ DMF}$ **48**

Cleavage

(1) **48** $\xrightarrow[25°,\ 1\text{–}5\ h,\ >90\%]{n\text{-}Bu_4N^+F^-,\ THF^{a}}$ ROH

(2) **48** $\xrightarrow[25°,\ 3\ h,\ 71\%]{3\%\ methanolic\ hydrogen\ chloride^{a}}$ ROH

(3) **48** $\xrightarrow[25°,\ 7\ h,\ 93\%]{5\ N\ NaOH/EtOH^a}$ ROH

(4) **48** $\xrightarrow{C_5H_5\overset{+}{N}H\ F^-,\ THF^b}$ ROH

ROH = an allylic alcohol

t-Butyldiphenylsilyl ethers are stable to K_2CO_3/CH_3OH, to 9 *M* NH_4OH, 60°, 2 h, and to $NaOCH_3$(cat.) /CH_3OH, 25°, 24 h. A *t*-butyldiphenylsilyl ether is stable to 80% acetic acid, used to cleave *t*-butyldimethylsilyl, triphenylmethyl, and tetrahydropyranyl ethers. It is also stable to HBr/HOAc, 12°, 2 min, and to 25–75% aq HCO_2H, 25°, 2–6 h. It is stable to concd HCl, 25°, 24 h, and to 50% aq CF_3CO_2H, 25°, 15 min (conditions used to form and cleave acetals). *t*-Butyldiphenylsilyl ethers are stable to oxidation [DMSO/1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide · HCl, 25°, 12 h] and to reduction [20% $Pd(OH)_2$-C; $(i\text{-}C_4H_9)_2AlH$].[a]

[a] S. Hanessian and P. Lavallee, *Can. J. Chem.*, **53**, 2975 (1975); **55**, 562 (1977).

[b] K. C. Nicolaou, S. P. Seitz, M. R. Pavia, and N. A. Petasis, *J. Org. Chem.*, **44**, 4011 (1979).

49. Methyldiisopropylsilyl Ether: $ROSiCH_3[CH(CH_3)_2]_2$, 49

Compound **49** is one in a series of silyl ethers prepared to study selective protection of 2′-, 3′-, and 5′-OH groups in nucleosides.[a]

***Formation* (→) / *Cleavage* (←)[a]**

ROH $\underset{\text{1.5–6 h, 100\%}}{\overset{\text{ClSiMe-}i\text{-}Pr_2\text{/imidazole, DMF}}{\rightleftarrows}}$ **49**

[a] K. K. Ogilvie, E. A. Thompson, M. A. Quilliam, and J. B. Westmore, *Tetrahedron Lett.*, 2865 (1974).

50. Methyldi-*t*-butylsilyl Ether: $ROSiCH_3(t\text{-}C_4H_9)_2$, 50

***Formation*[a]**

ROH + $t\text{-}Bu_2MeSiOClO_3$ $\xrightarrow[99\%]{CH_3CN/Py}$ **50**

***Cleavage*[a]**

(1) **50** $\xrightarrow{BF_3/CH_2Cl_2}$ $[ROBF_2]$ $\xrightarrow[0°,\ 30\ min,\ 94\%]{NaHCO_3,\ H_2O}$ ROH

(2) **50** + 1% HCl/95% EtOH $\xrightarrow[0\%]{25°,\ 3\ days}$ or $\xrightarrow[50\%]{90°,\ 24\ h}$ ROH

ROH = primary, secondary, or tertiary alcohol

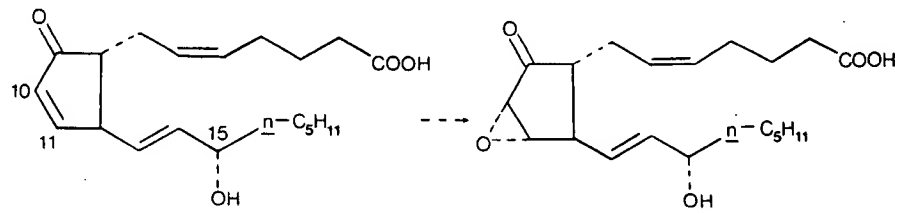
Compound **50** is more stable to acidic hydrolysis than is a tetrahydropyranyl or *t*-butyldimethylsilyl ether prepared from a primary or secondary alcohol. It is stable to basic hydrolysis (e.g., 5% NaOH, EtOH, 80°, 3 days).[a]

[a] T. J. Barton and C. R. Tully, *J. Org. Chem.*, **43**, 3649 (1978).

51. Tribenzylsilyl Ether: $ROSi(CH_2C_6H_5)_3$, 51

52. Tri-*p*-xylylsilyl Ether: $ROSi(CH_2C_6H_4\text{-}p\text{-}CH_3)_3$, 52

To control the stereochemistry of epoxidation at the 10,11-double bond in intermediates in prostaglandin syntheses, a bulky protective group was used for the C_{15}-OH group. Epoxidation of compound **52** yielded 88% α-oxide; epoxidation of **51** was less selective.[a]



***Formation* (→) / *Cleavage* (←)[a]**

ROH $\underset{\text{HOAc/THF/H}_2\text{O (3:1:1)}}{\overset{\text{ClSi(CH}_2\text{C}_6\text{H}_4\text{-}p\text{-Y)}_3\text{, DMF, 2,6-lutidine}}{\rightleftarrows}}$ **51** or **52**

ROH = PGA_2; Y = H, Me (**51** and **52**, respectively)

[a] E. J. Corey and H. E. Ensley, *J. Org. Chem.*, **38**, 3187 (1973)

53. Triisopropylsilyl Ether: $ROSi[CH(CH_3)_2]_3$, 53

Compound **53**, like compound **49**, was designed to study selective protection of 2′-, 3′-, and 5′-hydroxy groups in nucleosides. Triisopropylchlorosilane reacts almost exclusively with the primary 5′-OH group to form compound **53** (imidazole, DMF, 82% yield). Compound **53** is cleaved by acidic hydrolysis (0.01 *N* HCl/EtOH, 90°, 15 min, 100% yield).[a]

[a] K. K. Ogilvie, E. A. Thompson, M. A. Quilliam, and J. B. Westmore, *Tetrahedron Lett.*, 2865 (1974).

54. Triphenylsilyl Ether: $ROSi(C_6H_5)_3$, 54

***Formation* (→) / *Cleavage* (←)**[a]

$$\text{ROH} \underset{\text{HOAc-H}_2\text{O-THF (3:1:1)}}{\overset{\text{Ph}_3\text{SiBr, Py}}{\underset{-40°,\ 15\ \text{min}}{\rightleftharpoons}}} \textbf{54}$$
$$70°,\ 3\ \text{h},\ 70\%$$

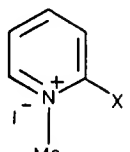
ROH = prostaglandin derivative

[a] H. Nakai, N. Hamanaka, H. Miyake, and M. Hayashi, *Chem. Lett.*, 1499 (1979).

ESTERS

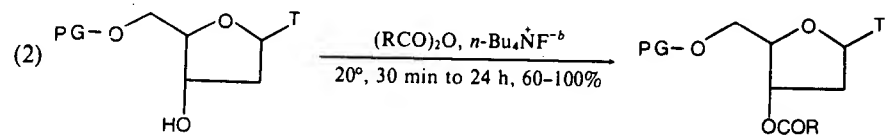
Esters and carbonates, in general prepared from an alcohol and an acid chloride or acid anhydride, or chloroformate, respectively, and cleaved by basic hydrolysis, complement ethers, cleaved by acidic hydrolysis, as protective group derivatives for alcohols. Some of the general methods used to prepare (see Chapter 5, Newer Methods of Formation, eqs. 2, 8, and 9) and cleave (Chapter 5, Newer Methods of Cleavage, eqs. 3 and 4) esters of carboxylic acids can be used to protect hydroxyl groups. Other general methods of formation (eqs. 1–3) and cleavage (eqs. 4–6) are as follows:

(1) $\text{ROH} + \text{R′COOH} \xrightarrow[\text{reflux, 3 h, 62–97\%}]{\text{Me}\ ,\ n\text{-Bu}_3\text{N, CH}_2\text{Cl}_2{}^a} \text{R′COOR}$



R = Et, *t*-Bu, Ph, $PhCH_2$, PhCH(Me), $PhCH{=}CHCH_2$

R′ = Me, *t*-Bu, Ph, $PhCH_2$, $PhCH{=}CH$

(2) 

R = Me, *t*-Bu, Ph

PG = protective group

(3) $\text{ROH} + o\text{-BrCH}_2\text{C}_6\text{H}_4\text{COOCOR′} \xrightarrow[85–100\%]{80–145°,\ 26\ \text{min to 10 h}^c} \text{ROCOR′}$

R = Et, *t*-Bu, Ph, $PhCH_2$

R′ = Et, Pr, *i*-Pr, *t*-Bu, Ph

(4) $\text{ROCOR′} + \text{H}_2\text{NNH}_2 \xrightarrow[\text{good yields}]{\text{HOAc/Py (1:4)}^d} \text{ROH}$

R′ = Me, Ph

ROH = nucleosides

(5) $\text{ROCOR′} \xrightarrow[2\ \text{h}]{\text{Na or Li/NH}_3,\ \text{Et}_2\text{O}} \xrightarrow{\text{NH}_4\text{Cl}} \text{ROH, 70–90\%}^e$

ROH = primary, secondary alcohol

R′ = Ph, *t*-Bu

(6) $\text{ROCOR′} \xrightarrow{\text{LiAlH}_4{}^f} \text{ROH, high yields}$

Cleavage of an ester by reduction with lithium aluminum hydride is a satisfactory method if no other functional group is present that is reactive to the reagent.

Esters that are most useful as alcohol protective groups are listed in Reactivity Chart 2.[g]

[a] T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, *Chem. Lett.*, 1045 (1975).
[b] S. L. Beaucage and K. K. Ogilvie, *Tetrahedron Lett.*, 1691 (1977).
[c] H. Horimoto, S. Takimoto, T. Katsuki, and M. Yamaguchi, *Chem. Lett.*, 145 (1979).
[d] Y. Ishido, N. Nakazaki, and N. Sakairi, *J. Chem. Soc., Perkin Trans. I*, 2088 (1979).

[e] H. W. Pinnick and E. Fernandez, *J. Org. Chem.*, **44**, 2810 (1979).

[f] For example, see S. P. Tanis and K. Nakanishi, *J. Am. Chem. Soc.*, **101**, 4398 (1979).

[g] See also: C. B. Reese, "Protection of Alcoholic Hydroxyl Groups and Glycol Systems," in *Protective Groups in Organic Chemistry*, J. F. W. McOmie, Ed., Plenum, New York and London, 1973, pp. 109–120; H. M. Flowers, "Protection of the Hydroxyl Group," in *The Chemistry of the Hydroxyl Group*, S. Patai, Ed., Wiley-Interscience, New York, 1971, Vol. 10/2, pp. 1012–1025; C. B. Reese, *Tetrahedron*, **34**, 3143–3179 (1978); V. Amarnath and A. D. Broom, *Chem. Rev.*, **77**, 183–217 (1977).

1. Formate Ester: ROCHO, 1

Formation

(1) $\mathrm{ROH} + 85\%\ \mathrm{HCOOH} \xrightarrow[93\%]{60^\circ,\ 1\ \mathrm{h}^a} \mathrm{ROCHO}$

ROH = steroid

(2) $\mathrm{ROH} + 70\%\ \mathrm{HCOOH/cat.\ HClO_4} \xrightarrow[\text{good yields}]{50\text{–}55^{\circ b}} \mathrm{ROCHO}$

ROH = steroid

(3) $\mathrm{ROH} + \mathrm{MeCOOCHO} \xrightarrow[-20^\circ,\ 80\text{–}100\%]{\mathrm{Py}^{c,d}} \mathrm{ROCHO}$

ROH = steroid,[c] nucleoside[d]

Cleavage

(1) $\mathrm{ROCHO} \xrightarrow[20^\circ,\ 3\ \mathrm{days}]{\mathrm{KHCO_3/aq\ MeOH}^e} \mathrm{ROH}$

(2) $\mathrm{ROCHO} \xrightarrow[22^\circ,\ 62\%]{\mathrm{dil\ NH_3,\ pH\ 11.2}^e} \mathrm{ROH}$

ROH = nucleoside

A formate ester can be cleaved selectively in the presence of an acetate [MeOH/reflux[d] or dil NH_3 (formate 100 times faster than acetate)[e]] or benzoate ester (dil NH_3).[e]

[a] H. J. Ringold, B. Löken, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 816 (1956).

[b] I. W. Hughes, F. Smith, and M. Webb, *J. Chem. Soc.*, 3437 (1949).

[c] F. Reber, A. Lardon, and T. Reichstein, *Helv. Chim. Acta*, **37**, 45 (1954).

[d] J. Žemlička, J. Beránek, and J. Smrt, *Collect. Czech. Chem. Commun.*, **27**, 2784 (1962).

[e] C. B. Reese and J. C. M. Stewart, *Tetrahedron Lett.*, 4273 (1968).

2. Benzoylformate Ester: $\mathrm{ROCOCOC_6H_5}$, 2

Compound **2** can be prepared from the 3′-hydroxy group in a deoxyribonucleotide by reaction with benzoyl chloroformate (anhyd Py, 20°, 12 h, 86% yield); it is cleaved by aqueous pyridine (20°, 12 h, 31% yield), conditions that do not cleave an acetate ester.[a]

[a] R. L. Letsinger and P. S. Miller, *J. Am. Chem. Soc.*, **91**, 3356 (1969).

3. Acetate Ester: $\mathrm{ROCOCH_3}$, 3

See also pp. 50–51.

Formation

(1) $\mathrm{ROH} + \mathrm{Ac_2O} \xrightarrow[20^\circ,\ 12\ \mathrm{h},\ \sim 100\%]{\mathrm{Py}^a} \mathrm{ROAc}$

ROH = 3′-hydroxynucleotide

(2) $\mathrm{ROH} + \mathrm{CH_3COCl} \xrightarrow[67\text{–}79\%]{25^\circ,\ 16\ \mathrm{h}^b} \mathrm{ROAc}$

ROH = a sugar

(3) $\mathrm{ROH} + (\mathrm{R'CO})_2\mathrm{O}\ \text{or}\ \mathrm{R'COCl} \xrightarrow[1\text{–}40\ \mathrm{h},\ 72\text{–}95\%]{\mathrm{DMAP},\ 24\text{–}80^{\circ c}} \mathrm{ROCOR'}$

ROH = hindered secondary or tertiary alcohol

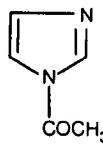
DMAP = 4-*N*,*N*-dimethylaminopyridine, 10^4 times as active an acylation catalyst as pyridine

R′ = Me, Et, Ph

(4) $\mathrm{ROH} + \mathrm{CH_3CO_2C_6F_5} \xrightarrow[80^\circ,\ 12\text{–}60\ \mathrm{h},\ 72\text{–}95\%]{\mathrm{Et_3N}^d} \mathrm{ROAc}$

ROH = aminoethanols

This reagent reacts with an amino group (25°, no Et_3N) to form an *N*-acetyl derivative in 80–90% yield.[d]

(5) $\mathrm{ROH} +$  $\cdot\,\mathrm{PtCl_2(C_2H_4)} \xrightarrow[51\text{–}87\%]{23^\circ,\ 0.5\text{–}144\ \mathrm{h}^e} \mathrm{ROAc}$

ROH = pyridinyl alcohol, $C_5H_4N(CH_2)_nCH_2OH$

Platinum(II) acts as a template to catalyze this acetylation.[e]

(6) $HOCH_2(CH_2)_nCH_2OH \xrightarrow[30\text{ h to 1 week, 60–95\%}]{HOAc/H_2SO_4,\ H_2O^f} AcOCH_2(CH_2)_nCH_2OH$

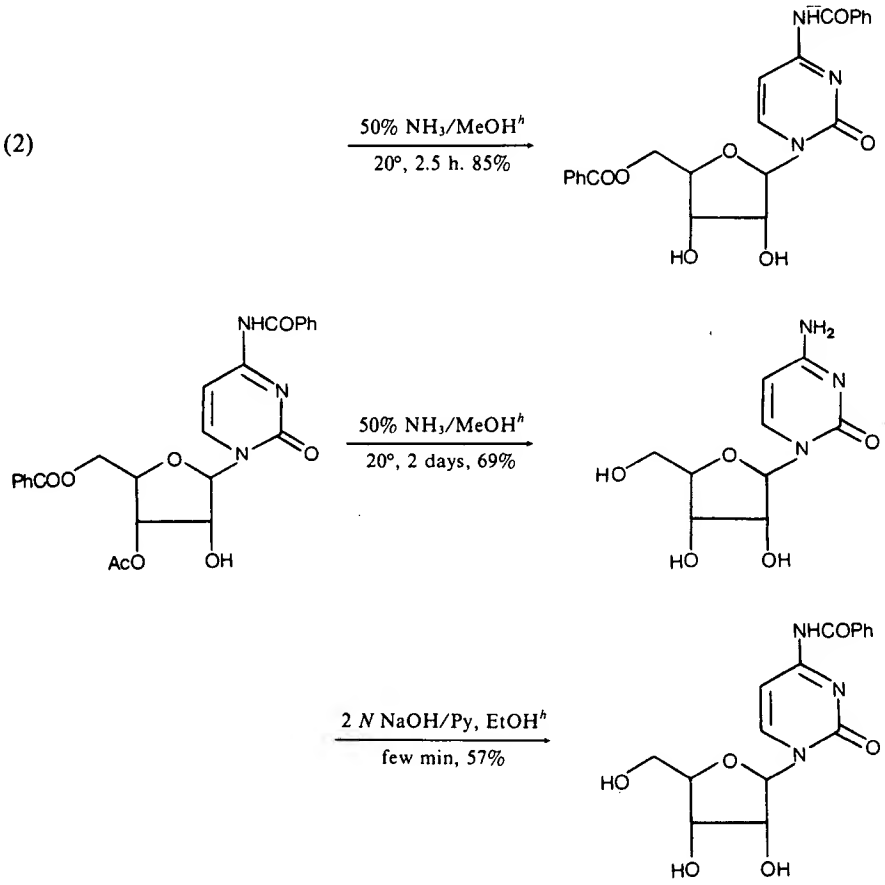
A monoacetate can be isolated by continuous extraction with organic solvents such as cyclohexane/CCl_4.[f]

Cleavage

(1) $ROAc \xrightarrow[20°,\ 1\text{ h},\ 100\%]{K_2CO_3/\text{aq MeOH}^g} ROH$

ROH = secondary or allylic alcohol

(2)



(3) $ROAc \xrightarrow[20°\text{ to reflux, 12 h}]{KCN/95\%\ EtOH^i} ROH,\ 93\%^j$

Potassium cyanide is a mild transesterification catalyst, suitable for acid- or base-sensitive compounds.[i,j]

[a] H. Weber and H. G. Khorana, *J. Mol. Biol.*, **72**, 219 (1972); R. I. Zhdanov and S. M. Zhenodarova, *Synthesis*, 222 (1975).
[b] D. Horton, *Org. Synth., Collect. Vol. V*, 1 (1973).
[c] G. Höfle, W. Steglich, and H. Vorbrüggen, *Angew. Chem., Inter. Ed. Engl.*, **17**, 569 (1978).
[d] L. Kisfaludy, T. Mohacsi, M. Low, and F. Drexler, *J. Org. Chem.*, **44**, 654 (1979).
[e] J. C. Chottard, E. Mulliez, and D. Mansuy, *J. Am. Chem. Soc.*, **99**, 3531 (1977).
[f] J. H. Babler and M. J. Coghlan, *Tetrahedron Lett.*, 1971 (1979).
[g] J. J. Plattner, R. D. Gless, and H. Rapoport, *J. Am. Chem. Soc.*, **94**, 8613 (1972).
[h] T. Neilson and E. S. Werstiuk, *Can. J. Chem.*, **49**, 493 (1971).
[i] K. Mori, M. Tominaga, T. Takigawa, and M. Matsui, *Synthesis*, 790 (1973).
[j] K. Mori and M. Sasaki, *Tetrahedron Lett.*, 1329 (1979).

4. Chloroacetate Ester: $ROCOCH_2Cl$, 4

Compound **4** can be prepared from an alcohol and the acid anhydride (nucleoside/Py, 0°, 2 h, 70–90% yield)[a] or acid chloride (prostaglandin/Py–Et_2O, 87% yield).[b] It is cleaved selectively in the presence of an acetate and benzoate ester by reaction with thiourea ($NaHCO_3$/EtOH, 70°, 5 h, 70% yield).[b] It can also be cleaved by reaction with $HSCH_2CH_2NH_2$, $H_2NCH_2CH_2NH_2$, or *o*-phenylenediamine,[a] and by basic hydrolysis (aq Py, pH 6.7, 20 h, 100% yield).[c]

[a] A. F. Cook and D. T. Maichuk, *J. Org. Chem.*, **35**, 1940 (1970).
[b] M. Naruto, K. Ohno, N. Naruse, and H. Takeuchi, *Tetrahedron Lett.*, 251 (1979).
[c] F. Johnson, N. A. Starkovsky, A. C. Paton, and A. A. Carlson, *J. Am. Chem. Soc.*, **86**, 118 (1964).

5. Dichloroacetate Ester: $ROCOCHCl_2$, 5

Compound **5** was prepared, by reaction with the acid chloride, to protect the hydroxyl group in 7-mandelamido-3-cephem-4-carboxylic acids. It is stable to mild acid and is cleaved at pH 9–9.5 (20°, 30 min).[a]

[a] J. R. E. Hoover, G. L. Dunn, D. R. Jakas, L. L. Lam, J. J. Taggart, J. R. Guarini, and L. Phillips, *J. Med. Chem.*, **17**, 34 (1974).

6. Trichloroacetate Ester: $ROCOCCl_3$, 6

Compound **6** was prepared to protect a C_{17}-hydroxy steroid (Cl_3CCOCl/Py, DMF, 20°, 2 days, 60–90% yield). A trichloroacetate ester can be cleaved in the

presence of an acetate ester (NH_3/EtOH, $CHCl_3$, 20°, 6 h, 81% yield) or a formate ester (KOH/MeOH, 72% yield).[a]

[a] V. Schwarz, *Collect. Czech. Chem. Commun.*, **27**, 2567 (1962).

7. Trifluoroacetate Ester: $ROCOCF_3$, 7

Trifluoroacetates, prepared[a] by reaction of an alcohol with the anhydride, are very readily hydrolyzed. In a series of nucleoside esters a trifluoroacetate is hydrolyzed immediately in 100% yield at 20°, pH 7.[b] A hindered alcohol was protected as a trifluoroacetate by reaction with pertrifluoroacetic acid (CF_3CO_3H, 20°, 4 h, 83% yield); trifluoroacetic acid did not form a trifluoroacetate.[c]

[a] A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **37**, 443 (1954).

[b] F. Cramer, H. P. Bär, H. J. Rhaese, W. Sänger, K. H. Scheit, G. Schneider, and J. Tennigkeit, *Tetrahedron Lett.*, 1039 (1963).

[c] G. W. Holbert and B. Ganem, *J. Chem. Soc., Chem. Commun.*, 248 (1978).

8. Methoxyacetate Ester: $ROCOCH_2OCH_3$, 8

Compound **8**, prepared by reaction with the acetyl chloride to protect nucleosides, is selectively cleaved (aq NH_3 or NH_3/MeOH, 78% yield) in the presence of acetate or benzoate esters; a methoxyacetate is cleaved 20 times faster than an acetate.[a]

[a] C. B. Reese and J. C. M. Stewart, *Tetrahedron Lett.*, 4273 (1968).

9. Triphenylmethoxyacetate Ester: $ROCOCH_2OC(C_6H_5)_3$, 9

Compound **9** was prepared in 53% yield from a nucleoside and the sodium acetate ($Ph_3COCH_2CO_2Na$/*i*-Pr_3-$C_6H_2SO_2Cl$, Py) as a derivative that could be easily detected (i.e., it has a distinct orange-yellow color after it is sprayed with ceric sulfate). It is readily cleaved by NH_3/MeOH (100% yield).[a]

[a] E. S. Werstiuk and T. Neilson, *Can. J. Chem.*, **50**, 1283 (1972).

10. Phenoxyacetate Ester: $ROCOCH_2OC_6H_5$, 10

Compound **10**, prepared to protect nucleosides by reaction with the anhydride, is selectively cleaved by aqueous or methanolic ammonia in the presence of acetate or benzoate esters; it is 50 times as labile to aqueous ammonia as an acetate ester.[a]

[a] C. B. Reese and J. C. M. Stewart, *Tetrahedron Lett.*, 4273 (1968).

11. *p*-Chlorophenoxyacetate Ester: $ROCOCH_2OC_6H_4$-*p*-Cl, 11

Compound **11**, prepared to protect a nucleoside by reaction with the acetyl chloride, is cleaved by 0.2 *M* NaOH/dioxane–H_2O, 0°, 30 s.[a]

[a] S. S. Jones and C. B. Reese, *J. Am. Chem. Soc.*, **101**, 7399 (1979).

12. 2,6-Dichloro-4-methylphenoxyacetate Ester: $ROCOCH_2OC_6H_2$-2,6-Cl_2-4-CH_3, 12

13. 2,6-Dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate Ester: $ROCOCH_2OC_6H_2$-2,6-Cl_2-4-$C(CH_3)_2CH_2C(CH_3)_3$, 13

14. 2,4-Bis(1,1-dimethylpropyl)phenoxyacetate Ester: $ROCOCH_2OC_6H_3$-2,4-$[C(CH_3)_2CH_2CH_3]_2$, 14

Compounds **12**, **13**, and **14** were developed to protect nucleosides. They are prepared by reaction with the acetyl chloride and cleaved by dilute ammonia.[a]

[a] C. B. Reese, *Tetrahedron*, **34**, 3143 (1978).

15. Chlorodiphenylacetate Ester: $ROCOCCl(C_6H_5)_2$, 15

Compound **15** was prepared in 87% yield from a nucleoside and the acetyl chloride. It is cleaved by methanolic ammonia (66 h, 68% yield).[a]

[a] A. F. Cook and D. T. Maichuk, *J. Org. Chem.*, **35**, 1940 (1970).

16. *p*-Ⓟ-Phenylacetate Ester: $ROCOCH_2C_6H_4$-*p*-Ⓟ, 16

Monoprotection of a symmetrical diol can be effected by reaction with a polymer-supported phenylacetyl chloride. The free hydroxyl group is then converted to an ether and the phenylacetate cleaved by aqueous ammonia–dioxane, 48 h.[a]

$$HO(CH_2)_nOH + p\text{-Ⓟ-}C_6H_4CH_2COCl \xrightarrow{Py} HO(CH_2)_nOCOCH_2C_6H_4\text{-}p\text{-Ⓟ}$$

n = 2, 4, 6, 8, 10

Ⓟ = polystyrene-divinylbenzene copolymer

[a] J. Y. Wong and C. C. Leznoff, *Can. J. Chem.*, **51**, 2452 (1973).

17. 3-Phenylpropionate Ester: $ROCOCH_2CH_2C_6H_5$, 17

Compound **17** has been used in nucleoside syntheses.[a] It is cleaved by α-chymotrypsin[a] (37°, 8–16 h, 70–90% yield).[b]

[a] H. S. Sachdev and N. A. Starkovsky, *Tetrahedron Lett.*, 733 (1969).
[b] A. T.-Rigby, *J. Org. Chem.*, **38**, 977 (1973).

18. 3-Benzoylpropionate Ester: $ROCOCH_2CH_2COC_6H_5$, 18

***Formation* (→) / *Cleavage* (←)**[a]

$$ROH \underset{\text{20°, 12 h, ~100%}}{\overset{\text{PhCO(CH}_2)_2\text{CO}_2\text{H/DCC, Py; 20°, 3 h, 50–65%}}{\rightleftharpoons}} \mathbf{18}$$

ROH = nucleoside

An acetate ester is stable to these cleavage conditions.[a]

[a] R. L. Letsinger and P. S. Miller, *J. Am. Chem. Soc.*, **91**, 3356 (1969).

19. Isobutyrate Ester: $ROCOCH(CH_3)_2$, 19

Isobutyric anhydride reacts with deoxyguanosine ($Et_4N^+OH^-$, 20°, 48 h) to form the *N*,3′,5′-triisobutyryl derivative. The isobutyrate esters are cleaved by basic hydrolysis (2 *M* NaOH/EtOH, 0°, 15 min, 100% yield), conditions that do not cleave the *N*-isobutanamide. Isobutyrate esters are stable to potassium bicarbonate.[a]

[a] H. Büchi and H. G. Khorana, *J. Mol. Biol.*, **72**, 251 (1972).

20. Monosuccinoate Ester: $ROCOCH_2CH_2COOH$, 20

A $C_{3,12}$-dihydroxy steroid was treated with succinic anhydride/Py, 3 h, to form the C_3-monosuccinoate ester in 55% yield. The C_{12}-hydroxy group was oxidized (CrO_3/HOAc) and the succinoate cleaved by basic hydrolysis (KOH/MeOH, reflux, 2 h, 78% yield).[a]

[a] P. L. Julian, C. C. Cochrane, A. Magnani, and W. J. Karpel, *J. Am. Chem. Soc.*, **78**, 3153 (1956).

21. 4-Oxopentanoate (Levulinate) Ester: $ROCOCH_2CH_2COCH_3$, 21

Formation

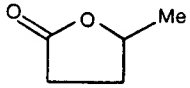
(1) $ROH + (CH_3COCH_2CH_2CO)_2O \xrightarrow[\text{24 h, 70–85%}]{\text{Py, 25°}[a]} \mathbf{21}$

ROH = steroids, nucleosides, . . .

(2) $ROH + CH_3COCH_2CH_2CO_2H \xrightarrow[96\%]{\text{DCC/DMAP}[b]} \mathbf{21}$

ROH = nucleoside

Cleavage

(1) **21** $\xrightarrow[\text{20°, 20 min, 80–95%}]{\text{NaBH}_4\text{/H}_2\text{O, pH 5–8}[a]}$ ROH +  , water soluble

(2) **21** $\xrightarrow[\text{2 min, 100\%}]{\text{0.5 } M \text{ H}_2\text{NNH}_2\text{/H}_2\text{O, Py, HOAc}[b]}$ ROH

[a] A. Hassner, G. Strand, M. Rubinstein, and A. Patchornik, *J. Am. Chem. Soc.*, **97**, 1614 (1975).
[b] J. H. van Boom and P. M. J. Burgers, *Tetrahedron Lett.*, 4875 (1976).

22. Pivaloate Ester: $ROCOC(CH_3)_3$, 22

A pivaloate ester is formed selectively from a primary hydroxyl group (i.e., from the 5′-OH in a nucleoside) by reaction with pivaloyl chloride/Py (0–75°, 2.5 days, 99% yield).[a]

Cleavage

(1) **22** $\xrightarrow[\text{20°, 4 h}]{\text{Bu}_4\text{N}^+\text{OH}^-[b]}$ ROH

ROH = carbohydrate

(2) **22** $\xrightarrow[\text{20°, } t_{1/2} = \text{3 h}]{\text{aq MeNH}_2[c]}$ ROH

ROH = uridine

An acetate ester can be selectively cleaved by NH_3/MeOH in the presence of a pivaloate ester.[c]

(3) **22** $\xrightarrow[20°,\ 12\ h,\ 58\%]{0.5\ N\ NaOH/EtOH,\ H_2O^d}$ ROH

ROH = nucleoside

(4) **22** $\xrightarrow{Li/NH_3,\ Et_2O}\ \xrightarrow{NH_4Cl}$ ROH, 70–85%[e]

(5) **22** $\xrightarrow[20°]{MeLi,\ Et_2O^f}$ ROH

(6) **22** $\xrightarrow[20°,\ 3\ h,\ 94\%]{KO\text{-}t\text{-}Bu/H_2O\ (8:2)^g}$ ROH

This method (using "anhydrous hydroxide") also cleaves tertiary amides.[g]

[a] M. J. Robins, S. D. Hawrelak, T. Kanai, J.-M. Siefert, and R. Mengel, *J. Org. Chem.*, **44**, 1317 (1979).
[b] C. A. A. van Boeckel and J. H. van Boom, *Tetrahedron Lett.*, 3561 (1979).
[c] B. E. Griffin, M. Jarman, and C. B. Reese, *Tetrahedron*, **24**, 639 (1968).
[d] K. K. Ogilvie and D. J. Iwacha, *Tetrahedron Lett.*, 317 (1973).
[e] H. W. Pinnick and E. Fernandez, *J. Org. Chem.*, **44**, 2810 (1979).
[f] B. M. Trost, S. A. Godleski, and J. L. Belletire, *J. Org. Chem.*, **44**, 2052 (1979).
[g] P. G. Gassman and W. N. Schenk, *J. Org. Chem.*, **42**, 918 (1977).

23. Adamantoate Ester: ROCO-1-adamantyl, 23

Compound **23** is formed selectively from a primary hydroxyl group (i.e., from the 5′-OH in a ribonucleoside) by reaction with adamantoyl chloride/Py (20°, 16 h). It is cleaved by alkaline hydrolysis (0.25 *N* NaOH, 20 min), but is stable to milder alkaline hydrolysis (e.g., NH_3/MeOH), conditions that cleave an acetate ester.[a]

[a] K. Gerzon and D. Kau, *J. Med. Chem.*, **10**, 189 (1967).

24. Crotonate Ester: ROCOCH=CHCH$_3$, 24

25. 4-Methoxycrotonate Ester: ROCOCH=CHCH$_2$OCH$_3$, 25

Compounds **24** and **25**, prepared to protect a primary hydroxyl group in nucleosides, are cleaved by hydrazine (MeOH/Py, 2 h). Compound **25** (R = nucleoside) is 100-fold more reactive to hydrazinolysis and 2-fold less reactive to alkaline hydrolysis than the corresponding acetate.[a]

[a] R. Arentzen and C. B. Reese, *J. Chem. Soc., Chem. Commun.*, 270 (1977).

26. (*E*)-2-Methyl-2-butenoate (Tigloate) Ester: ROCO—C(CH$_3$)=C(CH$_3$)—H, 26

A tigloate ester, prepared in 80% yield to protect a hydroxy steroid is oxidized (OsO_4/HIO_4) to an α-keto ester that is cleaved by mild basic hydrolysis (pH 8.5, 12 h, 90% yield).[a]

[a] S. M. Kupchan, A. D. J. Balon, and E. Fujita, *J. Org. Chem.*, **27**, 3103 (1962).

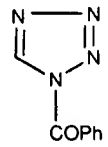
27. Benzoate Ester: ROCOC$_6$H$_5$, 27

Formation

(1) ROH $\xrightarrow[18°,\ 2\ days,\ \rightarrow\ 60°,\ 1\ h]{PhCOCl\ or\ (PhCO)_2O/Py^a}$ ROCOPh

ROH = carbohydrates

Regioselective benzoylation of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside can be effected by phase transfer catalysis (e.g., PhCOCl/*n*-$Bu_4N^+Cl^-$, 40% NaOH, C_6H_6, 69% yield of the 2-benzoate; PhCOCl/*n*-$Bu_4N^+Cl^-$, 40% NaOH, HMPA, 62% yield of the 3-benzoate).[b]

(2) ROH +  $\xrightarrow[20°,\ 15\ min,\ 90\%]{Et_3N,\ DMF^c}$ ROCOPh

ROH = nucleoside

(3) ROH + PhCOCN $\xrightarrow[5\ min\ to\ 2\ h,\ >\ 80\%]{Et_3N/CH_3CN^d}$ ROCOPh

ROH = steroids,[d] sugars[e]

Selective formation of benzoate esters, determined by steric factors, can be effected by reaction of the hydroxy compound with benzoyl cyanide. In hydroxy steroids the order of reactivity is C-21 > -17β > -3β > -6α,-3α >> -20α > -20β > -7β >> -6β > -22β > -22α.[d]

(4) MeOH + PhCOCF(CF$_3$)$_2$ $\xrightarrow[20°,\ 30\ min,\ 90\%]{TMEDA^f}$ ROCOPh

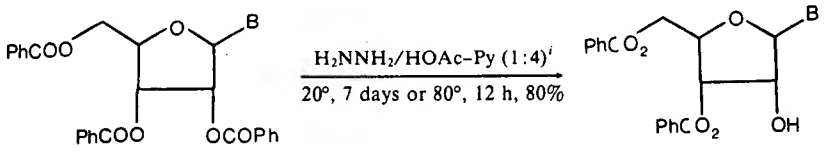
This reagent reacts with amines to form benzamides in high yields.[f]

Cleavage

Benzoate esters are more stable to hydrolysis than acetate esters.

(1) $ROCOPh \xrightarrow[20°,\ 50\ min,\ 90\%]{1\%\ NaOH/MeOH^{g}} ROH$

(2) $ROCOPh \xrightarrow[reflux,\ 20\ h,\ 86\%]{Et_3N/MeOH/H_2O\ (1:5:1)^{h}} ROH$

(3) 

Regioselective cleavage of the 2′-benzoate has been effected by these conditions.[i]

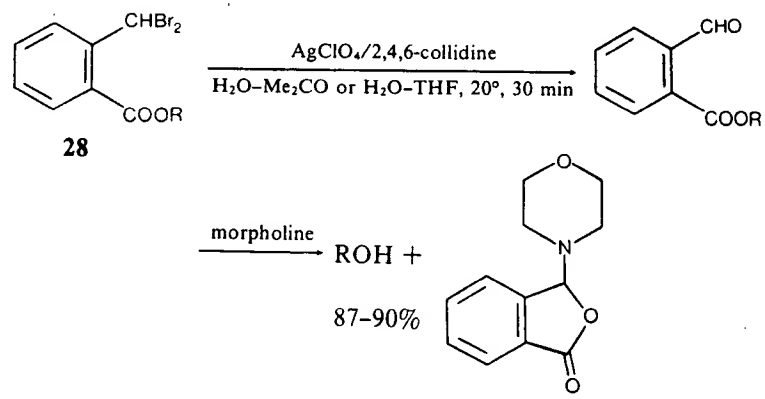
(4) A benzoate ester can be cleaved in 60–90% yield by electrolytic reduction at −2.3 V.[j]

[a] M. Gyr and T. Reichstein, *Helv. Chim. Acta*, **28**, 226 (1945); A. H. Haines, *Adv. Carbohydr. Chem. Biochem.*, **33**, 11 (1976).
[b] W. Szeja, *Synthesis*, 821 (1979).
[c] J. Stawinski, T. Hozumi, and S. A. Narang, *J. Chem. Soc., Chem. Commun.*, 243 (1976).
[d] M. Havel, J. Velek, J. Pospíšek, and M. Souček, *Collect. Czech. Chem. Commun.*, **44**, 2443 (1979).
[e] A. Holý and M. Souček, *Tetrahedron Lett.*, 185 (1971).
[f] N. Ishikawa and S. Shin-ya, *Chem. Lett.*, 673 (1976).
[g] K. Mashimo and Y. Sato, *Tetrahedron*, **26**, 803 (1970).
[h] K. Tsuzuki, Y. Nakajima, T. Watanabe, M. Yanagiya, and T. Matsumoto, *Tetrahedron Lett.*, 989 (1978).
[i] Y. Ishido, N. Nakazaki, and N. Sakairi, *J. Chem. Soc., Perkin Trans. 1*, 2088 (1979).
[j] V. G. Mairanovsky, *Angew. Chem., Inter. Ed. Engl.*, **15**, 281 (1976).

28. *o*-(Dibromomethyl)benzoate Ester: $ROCOC_6H_4$-*o*-$CHBr_2$, 28.

Compound **28**, prepared to protect nucleosides by reaction with the benzoyl chloride (CH_3CN, 65–90% yield), can be cleaved under nearly neutral conditions. This is a good example of a "protected protective group." The cleavage involves conversion of the $—CHBr_2$ group to —CHO by silver ion–assisted hydrolysis. The benzoate group, ortho to the —CHO group, now is rapidly hydrolyzed by neighboring group participation (the morpholine and hydroxide ion-catalyzed hydrolyses of methyl 2-formylbenzoate are particularly rapid).[a]

Cleavage[a]



28

ROH = nucleoside

[a] J. B. Chattopadhyaya, C. B. Reese, and A. H. Todd, *J. Chem. Soc., Chem. Commun.*, 987 (1979).

29. *o*-(Methoxycarbonyl)benzoate Ester: $ROCOC_6H_4$-*o*-$COOCH_3$, 29

Compound **29** was prepared to protect the hydroxyl group in lactic acid during a synthesis of Val-Oxisoval-Val-Oxisoval-Val by reaction with the monomethyl ester monoacid chloride of phthalic acid (Et_3N, 20°, 12 h, 50–60% yield). It is cleaved by hydrazine (80°, 1 h, 40–60% yield).[a]

[a] G. Losse and H. Raue, *Chem. Ber.*, **98**, 1522 (1965).

30. *p*-Phenylbenzoate Ester: $ROCOC_6H_4$-*p*-C_6H_5, 30

Compound **30** was prepared to protect a hydroxyl group of a prostaglandin intermediate by reaction with the benzoyl chloride (Py, 25°, 1 h, 97% yield). It was a more crystalline, more readily separated derivative than 15 other esters that were investigated.[a]

[a] E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Am. Chem. Soc.*, **93**, 1491 (1971).

31. 2,4,6-Trimethylbenzoate (Mesitoate) Ester: $ROCOC_6H_2$-2,4,6-$(CH_3)_3$, 31

Formation

(1) $ROH + ClCOC_6H_2\text{-}2,4,6\text{-}Me_3 \xrightarrow[0°,\ 14\ h \rightarrow 23°,\ 1\ h,\ 95\%]{Py,\ CHCl_3^{a}} \mathbf{31}$

ROH = allylic alcohol

(2) $ROH + HOOCC_6H_2\text{-}2,4,6\text{-}Me_3 \xrightarrow[20°,\ 15\ min]{(CF_3CO)_2O,\ C_6H_6[b]} \mathbf{31}$

ROH = secondary alcohol

Cleavage

(1) $\mathbf{31} \xrightarrow[20°,\ 2\ h]{LiAlH_4,\ Et_2O[b]} ROH$

(2) $\mathbf{31} \xrightarrow[20°,\ 24\text{–}72\ h,\ 50\text{–}72\%]{\text{"anhydrous hydroxide"}[c]\ KO\text{-}t\text{-}Bu/H_2O\ (8:1)} ROH$

A mesitoate ester is stable to mild basic hydrolysis (2 *N* NaOH, 20°, 20 h; 12 *N* NaOH/EtOH, 50°, 15 min).[b]

[a] E. J. Corey, K. Achiwa, and J. A. Katzenellenbogen, *J. Am. Chem. Soc.*, **91**, 4318 (1969).
[b] I. J. Bolton, R. G. Harrison, B. Lythgoe, and R. S. Manwaring, *J. Chem. Soc. C*, 2944 (1971).
[c] P. G. Gassman and W. N. Schenk, *J. Org. Chem.*, **42**, 918 (1977).

32. *p*-Ⓟ-Benzoate Ester: $ROCOC_6H_4\text{-}p\text{-}$Ⓟ, 32

A primary hydroxyl group in a carbohydrate has been protected as a polymer-supported benzoate:

$$ROH + ClCOC_6H_4\text{-}p\text{-}CH{=}CH_2 \xrightarrow[\text{(polymerization)}]{\text{styrene, AIBN, 60°}[a]} \mathbf{32}$$

Ⓟ = styrene-divinylbenzene polymer

[a] R. D. Guthrie, A. D. Jenkins, and J. Stehlicek, *J. Chem. Soc. C*, 2690 (1971).

33. α-Naphthoate Ester: ROCO-α-naphthyl, 33

Compound **33**, prepared to protect primary and secondary hydroxyl groups in a glucose by reaction with naphthoyl chloride (NaH, DMF, −10°, 9 h, 76% yield), is cleaved by sodium benzyloxide ($PhCH_2ONa/PhCH_2OH$, 37°, 2 h, 83% yield).[a]

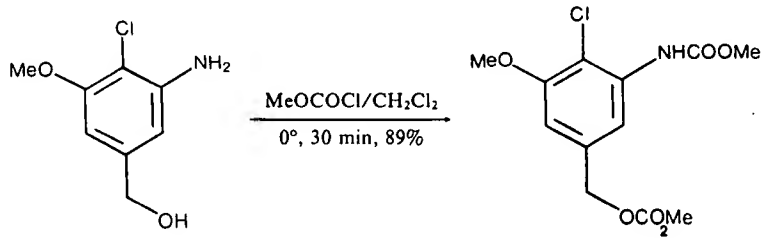
[a] I. Watanabe, T. Tsuchiya, T. Takase, S. Umezawa, and H. Umezawa, *Bull. Chem. Soc. Jpn.*, **50**, 2369 (1977).

Carbonates

Carbonates, like esters, are cleaved by basic hydrolysis (e.g., see alkyl methyl or ethyl carbonate, compounds **34** and **35**). Advantage, however, can be taken of the properties of the second alkyl group to effect selective cleavage of a carbonate in the presence of an ester (e.g., cleavage of a 2,2,2-trichloroethyl carbonate by reaction with zinc, or an *S*-benzylthiocarbonate by oxidation).

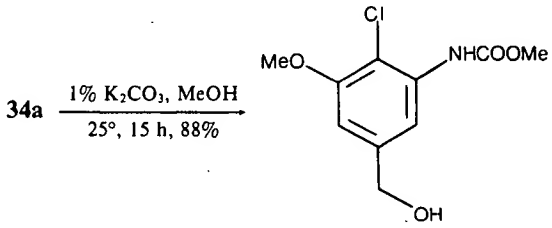
34. Alkyl Methyl Carbonate: $ROCOOCH_3$, 34

Formation[a]



34a

Cleavage[a]



[a] A. I. Meyers, K. Tomioka, D. M. Roland, and D. Comins, *Tetrahedron Lett.*, 1375 (1978).

35. Alkyl Ethyl Carbonate: $ROCOOC_2H_5$, 35

An ethyl carbonate, prepared and cleaved by conditions similar to those described for a methyl carbonate, was used to protect a hydroxyl group in glucose.[a]

[a] F. Reber and T. Reichstein, *Helv. Chim. Acta*, **28**, 1164 (1945).

36. Alkyl 2,2,2-Trichloroethyl Carbonate: $ROCOOCH_2CCl_3$, 36

Compound **36** can be cleaved under mild conditions by β-elimination with zinc or by electrolytic reduction.

Formation[a]

$$ROH + Cl_3CCH_2OCOCl \xrightarrow[20°,\ 12\ h]{Py} \mathbf{36}$$

Cleavage

(1) **36** $\xrightarrow[20°,\ 1\text{–}3\ h,\ 80\%]{Zn/HOAc^a}$ or $\xrightarrow[reflux,\ short\ time]{Zn/MeOH^a}$

or $\xrightarrow[20°,\ 3.5\ h,\ 100\%]{Zn\text{–}Cu/HOAc^b}$ ROH

(2) **36** $\xrightarrow[80\%]{-1.65\ V/MeOH,\ LiClO_4{}^c}$ cholesterol

A 2,2,2-tribromoethyl carbonate is cleaved by Zn–Cu/HOAc 10 times as fast as a trichloroethyl carbonate.[b]

[a] T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, 2555 (1967).
[b] A. F. Cook, *J. Org. Chem.*, **33**, 3589 (1968).
[c] M. F. Semmelhack and G. E. Heinsohn, *J. Am. Chem. Soc.*, **94**, 5139 (1972).

37. Alkyl Isobutyl Carbonate: $ROCOOCH_2CH(CH_3)_2$, 37

Compound **37** was prepared, by reaction with isobutyl chloroformate (Py, 20°, 3 days, 73% yield), to protect the 5′-OH group in thymidine. It was cleaved by acidic hydrolysis (80% HOAc, reflux, 15 min, 88% yield).[a]

[a] K. K. Ogilvie and R. L. Letsinger, *J. Org. Chem.*, **32**, 2365 (1967).

38. Alkyl Vinyl Carbonate: $ROCOOCH{=}CH_2$, 38

Formation **(→)** **/** ***Cleavage*** **(←)**[a]

$$ROH \underset{\xleftarrow[warm,\ 97\%]{Na_2CO_3,\ H_2O\text{–}dioxane}}{\xrightarrow[93\%]{CH_2{=}CHOCOCl/Py,\ CH_2Cl_2}} \mathbf{38}$$

ROH = cholesterol

Phenols can be protected under similar conditions. Amines are converted by these conditions to carbamates that are stable to alkaline hydrolysis with sodium carbonate. Carbamates are cleaved by acidic hydrolysis (HBr/MeOH, CH_2Cl_2, 8 h), conditions that do not cleave alkyl or aryl vinyl carbonates.[a]

[a] R. A. Olofson and R. C. Schnur, *Tetrahedron Lett.*, 1571 (1977).

39. Alkyl Allyl Carbonate: $ROCOOCH_2CH{=}CH_2$, 39

Compound **39** can be cleaved under mild, aprotic conditions:

Formation **(→)** **/** ***Cleavage*** **(←)**[a]

$$ROH \underset{\xleftarrow[55°,\ 4\ h,\ 87\text{–}95\%]{Ni(CO)_4/TMEDA,\ DMF}}{\xrightarrow[0 \rightarrow 20°,\ 2\ h,\ 90\%]{CH_2{=}CHCH_2OCOCl,\ Py,\ THF}} \mathbf{39}$$

ROH = primary, secondary alcohol

[a] E. J. Corey and J. W. Suggs, *J. Org. Chem.*, **38**, 3223 (1973).

40. Alkyl Cinnamyl Carbonate: $ROCOOCH_2CH{=}CHC_6H_5$, 40

A cinnamyl ester, used to protect a carboxyl group, is cleaved by the mild conditions shown below. The authors suggest that an alcohol (or an amine) can be protected as a cinnamyl carbonate, **40,** (or cinnamyl carbamate) and cleaved by the conditions, shown below, used to cleave an ester[a]:

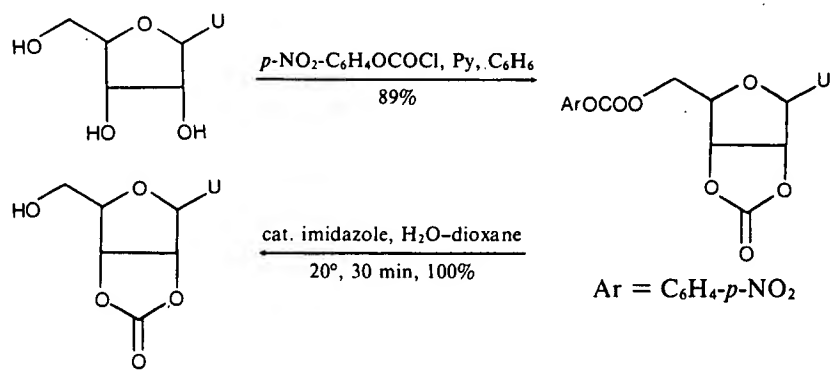
Cleavage[a]

$$RCO_2CH_2CH{=}CHPh \xrightarrow[23°,\ 2\text{–}4\ h]{Hg(OAc)_2/MeOH} \xrightarrow[23°,\ 12\text{–}16\ h]{KSCN,\ H_2O} RCOOH,\ 90\%$$

[a] E. J. Corey and M. A. Tius, *Tetrahedron Lett.*, 2081 (1977).

41. Alkyl *p*-Nitrophenyl Carbonate: $ROCOOC_6H_4$-*p*-NO_2, 41

Formation **(→)** **/** ***Cleavage*** **(←)**[a]



Acetates, benzoates, and cyclic carbonates are stable to these hydrolysis conditions. [Cyclic carbonates are cleaved by more alkaline conditions (e.g., dil NaOH, 20°, 5 min, or aq Py, warm, 15 min, 100% yield).][a]

[a] R. L. Letsinger and K. K. Ogilvie, *J. Org. Chem.*, **32**, 296 (1967).

42. Alkyl Benzyl Carbonate: $ROCOOCH_2C_6H_5$, 42

A benzyl carbonate was prepared in 83% yield from the sodium alkoxide of glycerol and benzyl chloroformate (20°, 24 h).[a] It is cleaved by hydrogenolysis (H_2/Pd-C, EtOH, 20°, 2 h, 2 atm, 76% yield)[a] and electrolytic reduction (−2.7 V, $R_4N^+X^-$, DMF, 70% yield).[b] A benzyl carbonate was used to protect the hydroxyl group in lactic acid during a peptide synthesis.[c]

[a] B. F. Daubert and C. G. King, *J. Am. Chem. Soc.*, **61**, 3328 (1939).
[b] V. G. Mairanovsky, *Angew. Chem., Inter. Ed. Engl.*, **15**, 281 (1976).
[c] G. Losse and G. Bachmann, *Chem. Ber.*, **97**, 2671 (1964).

43. Alkyl *p*-Methoxybenzyl Carbonate: $ROCOOCH_2C_6H_4$-*p*-OCH_3, 43

44. Alkyl 3,4-Dimethoxybenzyl Carbonate: $ROCOOCH_2C_6H_3$-3,4-$(OCH_3)_2$, 44

Compounds **43** and **44**, prepared to protect the hydroxyl group in cholesterol, are cleaved by oxidation with triphenylmethyl fluoroborate, $Ph_3C^+BF_4^-$: **43**, 0°, 6 min, 90% yield; **44**, 0°, 15 min, 90% yield.[a]

[a] D. H. R. Barton, P. D. Magnus, G. Smith, G. Streckert, and D. Zurr, *J. Chem. Soc., Perkin Trans. I*, 542 (1972).

45. Alkyl *o*-Nitrobenzyl Carbonate: $ROCOOCH_2C_6H_4$-*o*-NO_2, 45

46. Alkyl *p*-Nitrobenzyl Carbonate: $ROCOOCH_2C_6H_4$-*p*-NO_2, 46

Compounds **45** and **46** were prepared to protect a secondary hydroxyl group in a thienamycin precursor. Compound **45** was prepared from the chloroformate (DMAP, CH_2Cl_2, 0° → 20°, 3 h) and cleaved by irradiation, pH 7.[a] Compound **46** was prepared from the chloroformate (−78°, *n*-BuLi/THF, 85% yield) and cleaved by hydrogenolysis (H_2/Pd-C, dioxane–H_2O–EtOH–K_2HPO_4).[b] Compound **46** is also cleaved by electrolytic reduction (−1.1 V, $R_4N^+X^-$, DMF).[c]

[a] L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 8006 (1978).
[b] D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 313 (1978).
[c] V. G. Mairanovsky, *Angew. Chem., Inter. Ed., Engl.*, **15**, 281 (1976).

47. Alkyl *S*-Benzyl Thiocarbonate: $ROCOSCH_2C_6H_5$, 47

***Formation* (→) / *Cleavage* (←)**[a]

$$ROH \underset{\text{20°, 4 days, 50–55\%}}{\overset{\text{PhCH}_2\text{SCOCl/Py, 65–70\%}}{\rightleftharpoons}} \mathbf{47}$$

ROH = carbohydrate

[a] J. J. Willard, *Can. J. Chem.*, **40**, 2035 (1962).

Miscellaneous Esters

48. Alkyl *N*-Phenylcarbamate: $ROCONHC_6H_5$, 48

Formation[a]

$$ROH \xrightarrow[\text{20°, 2–3 h, ~100\%}]{\text{PhN=C=O, Py}} ROCONHPh$$

ROH = nucleoside

Cleavage

(1) $$ROCONHPh \xrightarrow[\text{reflux, 1.5 h, good yield}]{\text{NaOMe/MeOH}^b} ROH$$

(2) $$ROCONHPh \xrightarrow[\text{reflux, 3–4 h, 90\%}]{\text{LiAlH}_4\text{/THF or dioxane}^b} ROH$$

Carbamates are more stable to hydrolysis than esters.

(3) $$ROCONHR' \xrightarrow[\text{4–48 h, 25–80°}]{\text{Cl}_3\text{SiH/Et}_3\text{N, CH}_2\text{Cl}_2} \xrightarrow{H_2O} ROH,\ 80\text{–}95\%^c$$

ROH = primary, secondary, tertiary, allylic, propargylic, or benzyl alcohol

(4) Compound **48** is cleaved by passage through a trityl-cellulose column.[a]

[a] K. L. Agarwal and H. G. Khorana, *J. Am. Chem. Soc.*, **94**, 3578 (1972).
[b] H. O. Bouveng, *Acta Chem. Scand.*, **15**, 87, 96 (1961).
[c] W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **42**, 2781 (1977).

49. Alkyl *N*-Imidazolylcarbamate: ROCO—N(imidazole), 49

***Formation* (→) / *Cleavage* (←)**[a]

$$\text{ROH} \xrightarrow[20°,\ 20\ \text{h},\ 100\%]{\text{1,1'-carbonyldiimidazole, } CH_2Cl_2} \mathbf{49} \xleftarrow[20°,\ 12\ \text{h}]{Na_2CO_3,\ H_2O,\ \text{THF}}$$

ROH = tylosin precursor

[a] A. A. Nagel and L. A. Vincent, *J. Org. Chem.*, **44**, 2050 (1979).

50. Borate Ester: $(RO)_3B$, 50

Compound **50** was prepared, by reaction with boric acid (C_6H_6, reflux), to protect a hydroxyl group during a synthesis of dihydro-β-santalol. It is readily cleaved by hydrolysis under acidic, basic, or neutral conditions.[a] Borate esters can also be prepared by the following method:

Formation[b]

$$3\ \text{ROH} + BH_3 \cdot SMe_2 \xrightarrow[80\text{–}90\%]{25°,\ 1\ \text{h}} (RO)_3B$$

ROH = primary, secondary, tertiary, and aromatic alcohols

[a] W. I. Fanta and W. F. Erman, *J. Org. Chem.*, **37**, 1624 (1972).

[b] C. A. Brown and S. Krishnamurthy, *J. Org. Chem.*, **43**, 2731 (1978).

51. Nitrate Ester: $RONO_2$, 51

A nitrate ester is stable to the mildly acidic conditions that cleave acetals and ketals, and to the mildly basic conditions that cleave esters. Nitrates have been prepared to protect carbohydrates[a] and steroids[b] by reaction with nitric acid (50–100% yield).[c] In general nitrate esters are cleaved by reduction (e.g., with $LiAlH_4$; H_2/Raney Ni or H_2/Pd; Zn/or Fe/HOAc; or Na_2S),[a] or by nucleophilic displacement (with H_2NNH_2).[a] Irradiation may provide a milder method of cleavage[d]:

Cleavage[d]

$$RONO_2 \xrightarrow[1\ \text{h},\ 92\text{–}100\%]{h\nu,\ i\text{-PrOH}} \text{ROH}$$

ROH = carbohydrate

[a] J. Honeyman and J. W. W. Morgan, *Adv. Carbohydr. Chem.*, **12**, 117 (1957).

[b] J. F. W. Keana, in *Steroid Reactions*, C. Djerassi, Ed., Holden-Day, San Francisco, 1963, pp. 75–76.

[c] R. Boschan, R. T. Merrow, and R. W. Van Dolah, *Chem. Rev.*, **55**, 485 (1955).

[d] R. W. Binkley and D. J. Koholic, *J. Org. Chem.*, **44**, 2047 (1979).

52. Alkyl *N,N,N',N'*-Tetramethylphosphorodiamidate: $ROPO[N(CH_3)_2]_2$, 52

Protection of a hydroxyl group as a phosphorodiamidate has been suggested.[a] Compounds such as **52** are stable to a variety of reagents (e.g., MeLi/Et_2O, 25°, 2 h; $LiAlH_4$/Et_2O, 25°, 2 h; 1 *N* KOH/EtOH, reflux, 15 h; and 0.2 *N* HCl/acetone, 25°, 2 h). Compound **52** (R = 3β-cholestanyl) is cleaved by reaction with *n*-butyllithium (5 eq *n*-BuLi in TMEDA, 25°, 30 min, 100% yield).[a]

Formation[a]

$$\text{ROH} + (Me_2N)_2POCl \xrightarrow[25°,\ 1\text{–}2\ \text{h},\ 90\%]{n\text{-BuLi/THF, TMEDA}} \mathbf{52}$$

ROH = primary, secondary, tertiary alcohol

[a] R. E. Ireland, D. C. Muchmore, and U. Hengartner, *J. Am. Chem. Soc.*, **94**, 5098 (1972).

53. Alkyl 2,4-Dinitrophenylsulfenate: $ROSC_6H_3$-2,4-$(NO_2)_2$, 53

A nitrophenylsulfenate, cleaved by nucleophiles under very mild conditions, was developed as protection for a hydroxyl group during solid phase nucleotide synthesis.[a] Compound **53** is stable to acidic hydrolysis of acetonides prepared to protect 1,2-diols.[b]

Formation

$$\text{ROH} + ClSC_6H_3\text{-}2,4\text{-}(NO_2)_2 \xrightarrow[20°,\ 1\ \text{h},\ 70\text{–}85\%]{\text{Py/DMF}^a \text{ or } CH_2Cl_2{}^b} \mathbf{53}$$

Cleavage

(1) $$\mathbf{53} \xrightarrow[25°,\ 4\ \text{h},\ 63\text{–}80\%]{Nu^-/\text{MeOH},\ H_2O^a} \text{ROH}$$

Nu^- = $Na_2S_2O_3$, pH 8.9; NaCN, pH 8.9; Na_2S, pH 6.6; PhSH, pH 11.8.

(2) $$\mathbf{53} \xrightarrow[54\%]{H_2/\text{Raney Ni}^b} \text{or} \xrightarrow[5\ \text{h},\ 67\%]{Al/Hg(OAc)_2,\ \text{MeOH}^b} \text{ROH}$$

(3) An alkyl *o*-nitrophenylsulfenate is cleaved by electrolytic reduction (−1.0 V, DMF, $R_4N^+X^-$).[c]

[a] R. L. Letsinger, J. Fontaine, V. Mahadevan, D. A. Schexnayder, and R. E. Leone, *J. Org. Chem.*, **29**, 2615 (1964).

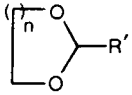
[b] K. Takiura, S. Honda, and T. Endo, *Carbohydr. Res.*, **21**, 301 (1972).

[c] V. G. Mairanovsky, *Angew. Chem., Inter. Ed. Engl.*, **15**, 281 (1976).

PROTECTION FOR 1,2- AND 1,3-DIOLS

cis-1,2-Diols (e.g., in carbohydrates[a] and nucleosides[b]), and *cis*- and *trans*-1,3-diols can be protected as cyclic acetals and ketals (e.g., dioxolanes or dioxanes) or cyclic ortho esters that are cleaved by acidic hydrolysis, or as cyclic esters (e.g., carbonates and boronates) that are cleaved by basic hydrolysis.[b]

Cyclic acetals and ketals are formed by reaction of the diol and a carbonyl compound in the presence of an acid catalyst. They are formed in moderate yield by reaction of a diol with an enol ether (eq. 1).[c]

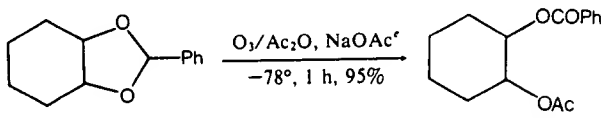
(1) $HO(CH_2)_nOH + CH_2{=}CHOR \xrightarrow[20°,\ 24\ h,\ 50\text{–}60\%]{KSF/CH_2Cl_2}$ 

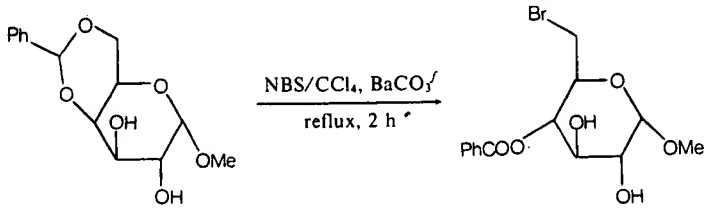
n = 2, 4, or 6; R = Et

enol ether = EtO-1-cyclohexenyl; dihydropyran

Depending on conditions either the kinetic or thermodynamic product can be isolated.[d]

Dioxanes and dioxolanes are stable to the alkaline conditions of *O*-alkylation or acylation, to reduction by lithium aluminum hydride or Na(Hg), and (with the exception of benzylidene acetals/ketals) to reduction by catalytic hydrogenation. Dioxanes and dioxolanes are stable to some oxidizing agents [e.g., CrO_3/Py; $NaIO_4$; $Pb(OAc)_4$, <80°; Ag_2O; $KMnO_4/OH^-$; $Al(O\text{-}i\text{-}Pr)_3$-acetone]. Benzylidene acetals react with O_3[e] or NBS[f] (eqs. 2 and 3).

(2) 

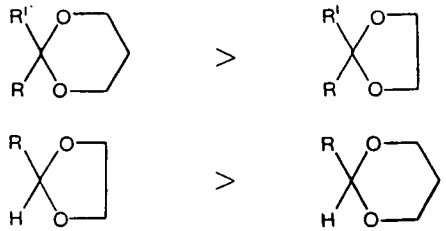
(3) 

Kinetic studies of acetal/ketal formation, from cyclohexanone, and hydrolysis (3×10^{-3} *N* HCl/dioxane–H_2O, 20°) indicate the following orders of reactivity[g]:

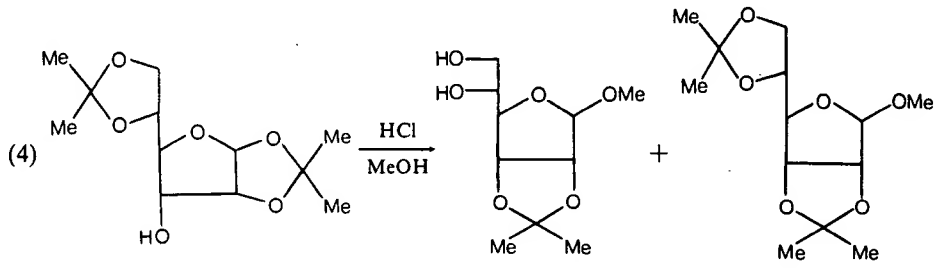
Formation

$$HOCH_2C(CH_3)_2CH_2OH > HO(CH_2)_2OH > HO(CH_2)_3OH$$

Cleavage



The relative rates of acid-catalyzed hydrolysis of some dioxolanes [dioxolane: aq HCl (1:1)] are 2,2-dimethyldioxolane: 2-methyldioxolane: dioxolane, 50,000:5,000:1.[h] Acidic hydrolysis of some cyclic acetals and ketals can lead to a mixture of products by migration of the dioxolane group (eq. 4).[d]

(4) 

Cyclic ortho esters are more readily cleaved by acidic hydrolysis than are cyclic acetals or ketals. A number of substituted cyclic acetals and ketals have been developed to provide wide variation in ease of removal.

Cyclic carbonates are prepared from a diol and phosgene or a chloroformate in the presence of base. Cyclic boronates, prepared by reaction of the diol with a boronic acid [e.g., $PhB(OH)_2$] in the presence of pyridine, are readily cleaved by water.

The most useful protective groups for diols are listed in Reactivity Chart 3; conventions that are used in this section are described on p. xii.[i]

[a] H. G. Fletcher, Jr., *Methods Carbohydr. Chem.*, **II**, 307 (1963); T. G. Bonner, *Methods Carbohydr. Chem.*, **II**, 309, 314 (1963); O. Th. Schmidt, *Methods Carbohydr. Chem.*, **II**, 318 (1963); A. N. de Belder, *Adv. Carbohydr. Chem.*, **20**, 219–302 (1965).

[b] V. Amarnath and A. D. Broom, *Chem. Rev.*, **77**, 183 (1977); C. B. Reese, *Tetrahedron*, **34**, 3143 (1978).

[c] V. M. Thuy and P. Maitte, *Bull. Soc. Chim. Fr.*, II-264 (1979).

[d] D. M. Clode, *Chem. Rev.*, **79**, 491 (1979).

[e] P. Deslongchamps, C. Moreau, D. Fréhel, and R. Chênevert, *Can. J. Chem.*, **53**, 1204 (1975).

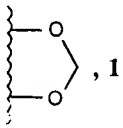
[f] S. Hanessian, *Carbohydr. Res.*, **2**, 86 (1966).

[g] M. S. Newman and R. J. Harper, *J. Am. Chem. Soc.*, **80**, 6350 (1958); S. W. Smith and M. S. Newman, *J. Am. Chem. Soc.*, **90**, 1249, 1253 (1968).

[h] P. Salomaa and A. Kankaanperä, *Acta Chem. Scand.*, **15**, 871 (1961).

[i] See also: C. B. Reese, "Protection of . . . Glycol Systems," in *Protective Groups in Organic Chemistry*, J. F. W. McOmie, Ed., Plenum, New York and London, 1973, pp. 120–135; H. M. Flowers, "Protection of the Hydroxyl Group," in *The Chemistry of the Hydroxyl Group*, S. Patai, Ed., Wiley-Interscience, New York, 1971, Vol. 10/2, pp. 1025, 1028–1035.

Cyclic Acetals and Ketals

1. Methylene Acetal:  , 1

Formation

(1) $C_6H_8(OH)_6 \xrightarrow[50°,\ 4\ days,\ 68\%]{40\%\ CH_2O,\ concd\ HCl^a}$ **1a**

1a = trismethylenedioxy derivative

(2) sugar $\xrightarrow[90°,\ 1\ h,\ good\ yield]{paraformaldehyde,\ H_2SO_4,\ HOAc^b}$ **1b**

1b = bismethylenedioxy derivative

(3) *cis*-cyclohexane-1,2-diol $\xrightarrow[50°,\ 12\ h,\ 62\%]{DMSO,\ NBS^c}$ **1**

(4) *cis*-cyclohexane-1,2-diol $\xrightarrow[0\text{–}30°,\ 40\ h,\ 46\%]{CH_2Br_2,\ NaH,\ DMF^d}$ **1**

Cleavage

(1) **1a** $\xrightarrow[-80°,\ 30\ min \rightarrow 20°]{BCl_3/CH_2Cl_2}$ $\xrightarrow[NaOAc]{Ac_2O}$ $C_6H_8(OAc)_6$, 61%[a]

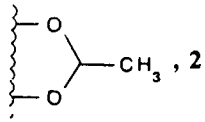
(2) **1b** $\xrightarrow[100°,\ 3\ h]{2\ N\ HCl^b}$ sugar

[a] T. G. Bonner, *Methods Carbohydr. Chem.*, **II**, 314 (1963).

[b] L. Hough, J. K. N. Jones, and M. S. Magson, *J. Chem. Soc.*, 1525 (1952).

[c] S. Hanessian, G. Y.-Chung, P. Lavallee, and A. G. Pernet, *J. Am. Chem. Soc.*, **94**, 8929 (1972).

[d] J. S. Brimacombe, A. B. Foster, B. D. Jones, and J. J. Willard, *J. Chem. Soc. C*, 2404 (1967).

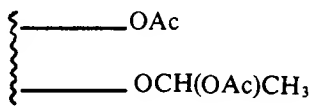
2. Ethylidene Acetal:  , 2

Formation

sugar $\xrightarrow[concd\ H_2SO_4,\ 2\text{–}3\ h,\ 60\%]{CH_3CHO,\ CH_3CH(OMe)_2,\ or\ paraldehyde^a}$ **2**

Cleavage

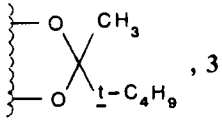
(1) **2** $\xrightarrow[reflux,\ 7\ h]{0.67\ N\ H_2SO_4,\ aq\ Me_2CO^a}$ sugar

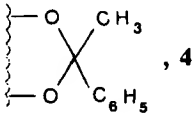
(2) **2** $\xrightarrow[20°,\ 5\ min,\ 60\%]{Ac_2O,\ cat.\ H_2SO_4^a}$ 

(3) **2** $\xrightarrow[reflux,\ 1.5\ h]{80\%\ HOAc^b}$ 1,2-diol

[a] T. G. Bonner, *Methods Carbohydr. Chem.*, **II**, 309 (1963).

[b] J. W. Van Cleve and C. E. Rist, *Carbohydr. Res.*, **4**, 82 (1967).

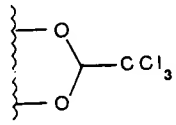
3. 1-*t*-Butylethylidene Ketal:  , 3

4. 1-Phenylethylidene Ketal:  , 4

Compounds **3** and **4** were prepared selectively from the C_4–C_6 1,3-diol in glucose by an acid-catalyzed transketalization reaction [e.g., $Me_3CC(OMe)_2CH_3$, TsOH/DMF, 24 h, 79% yield; $PhC(OMe)_2Me$, TsOH/DMF, 24 h, 90% yield,

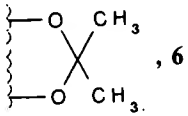
respectively]. They are cleaved by acidic hydrolysis—**3**: HOAc, 20°, 90 min, 100% yield; **4**: HOAc, 20°, 3 days, 100% yield.[a]

[a] M. E. Evans, F. W. Parrish, and L. Long, Jr., *Carbohydr. Res.*, **3**, 453 (1967).

5. 2,2,2-Trichloroethylidene Acetal:  , 5

Trichloroacetaldehyde (chloral) reacts with glucose in the presence of sulfuric acid to form two mono- and four diacetals (e.g., compound **5**). Compound **5** is cleaved by reduction [H_2/Raney Ni, 50% NaOH/EtOH, 15 min].[a] Compound **5** can probably be cleaved by reaction with Zn/HOAc [cf. $ROCH(R')OCH_2CCl_3$ cleaved by Zn/HOAc, NaOAc, 20°, 3 h, 90% yield[b]].

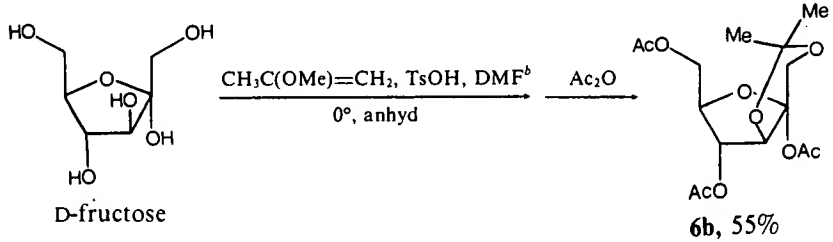
[a] S. Forsén, B. Lindberg, and B.-G. Silvander, *Acta Chem. Scand.*, **19**, 359 (1965).
[b] R. U. Lemieux and H. Driguez, *J. Am. Chem. Soc.*, **97**, 4069 (1975).

6. Acetonide (Isopropylidene Ketal):  , 6

Formation

(1) 1,3-diol $\xrightarrow[0°,\ 16\ h,\ 75\%]{CH_3C(OMe)=CH_2,\ dry\ HBr,\ CH_2Cl_2}$ **6a**

1,3-diol = erythronolide precursor

(2) 

D-fructose

6b, 55%

Under these conditions 2-methoxypropene reacts to form the kinetically controlled 1,3-*O*-isopropylidene, **6b**, instead of the thermodynamically more stable 1,2-*O*-isopropylidene.[b]

(3) sugar $\xrightarrow[24\ h]{Me_2C(OMe)_2,\ TsOH,\ DMF^c}$ **6c** + **6d**

79% 1.8%

sugar = methyl α-D-glucopyranoside

6c = methyl 4,6-*O*-isopropylidene-α-D-glucoside

6d = methyl 2,3:4,6-di-*O*-isopropylidene-α-D-glucoside

(4) sugar $\xrightarrow[36°,\ 5\ h,\ 60\text{–}70\%]{anhyd\ Me_2CO,\ FeCl_3^d}$ **6**

(5) nucleoside $\xrightarrow[3\text{–}5\ h,\ 90\text{–}100\%]{Me_2C(OMe)_2,\ cat.^e}$ **6**

cat. = di-*p*-nitrophenyl hydrogen phosphate

(6) nucleoside $\xrightarrow[25°,\ 12\ h,\ 90\text{–}100\%]{MeC(OEt)=CH_2,\ cat.\ HCl,\ DMF^f}$ **6**

(7) diol $\xrightarrow[10\text{–}30\ min,\ 80\text{–}85\%]{MeC(OSiMe_3)=CH_2,\ concd\ HCl\ or\ Me_3SiCl^g}$ **6**

diol = *cis*- or *trans*-*c*-C_6H_{10}-1,2-$(OH)_2$;

trans-*c*-C_7H_{12}-1,2-$(OH)_2$; acyclic diols

(8) The classical method of formation of an acetonide is by reaction of a diol with acetone and an acid catalyst.[h,i]

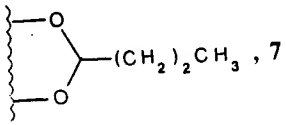
Cleavage

A variety of acid-catalyzed hydrolysis conditions have been required to cleave an acetonide:

i. **6a**, 1 *N* HCl/THF (1:1), 20°[a]
ii. **6**, 2 *N* HCl, 80°, 6 h[j]
iii. **6**, 60–80% HOAc, 25°, 2 h, 92% yield of *cis*-1,2-diol[k]
iv. **6**, 80% HOAc, reflux, 30 min, 78% yield of *trans*-1,2-diol[k]
v. **6**, TsOH/MeOH, 25°, 5 h[l]
vi. **6**, TsOH/MeOH, 25°, 1 day; a 2′,3′-ribonucleoside acetonide was not cleaved[m]
vii. **6**, Dowex 50-W(H^+), H_2O, 70°, excellent yield[n]
viii. **6**, BCl_3, 25°, 2 min, 100% yield[o]
ix. **6**, Br_2, Et_2O[p]

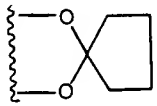
[a] E. J. Corey, S. Kim, S. Yoo, K. C. Nicolaou, L. S. Melvin, Jr., D. J. Brunelle, J. R. Falck, E. J. Trybulski, R. Lett, and P. W. Sheldrake, *J. Am. Chem. Soc.*, **100**, 4620 (1978).

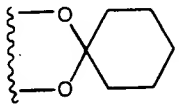
[b] E. Fanton, J. Gelas, and D. Horton, *J. Chem. Soc., Chem. Commun.*, 21 (1980).
[c] M. E. Evans, F. W. Parrish, and L. Long, Jr., *Carbohydr. Res.*, **3**, 453 (1967).
[d] P. P. Singh, M. M. Gharia, F. Dasgupta, and H. C. Srivastava, *Tetrahedron Lett.*, 439 (1977).
[e] A. Hampton, *J. Am. Chem. Soc.*, **83**, 3640 (1961).
[f] S. Chládek and J. Smrt, *Collect. Czech. Chem. Commun.*, **28**, 1301 (1963).
[g] G. L. Larson and A. Hernandez, *J. Org. Chem.*, **38**, 3935 (1973).
[h] O. Th. Schmidt, *Methods Carbohydr. Chem.*, **II**, 318 (1963).
[i] A. N. de Belder, *Adv. Carbohydr. Chem.*, **20**, 219 (1965).
[j] T. Ohgi, T. Kondo, and T. Goto, *Tetrahedron Lett.*, 4051 (1977).
[k] M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **34**, 3505 (1969).
[l] A. Ichihara, M. Ubukata, and S. Sakamura, *Tetrahedron Lett.*, 3473 (1977).
[m] J. Kimura and O. Mitsunobu, *Bull. Chem. Soc. Jpn.*, **51**, 1903 (1978).
[n] P.-T. Ho, *Tetrahedron Lett.*, 1623 (1978).
[o] T. J. Tewson and M. J. Welch, *J. Org. Chem.*, **43**, 1090 (1978).
[p] A. N. de Belder, *Adv. Carbohydr. Chem.*, **20**, 219–302 (1963), see p. 235.

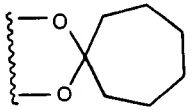
7. Butylidene Acetal:  , **7**

Compound **7**, prepared from a 1,2-diol by reaction with butyraldehyde (cat. concd HCl/DMF, 24 h), is cleaved by acidic hydrolysis (cat. concd HCl/CF_3CO_2H, EtOH, H_2O, 65°, 5 h, ~100% yield).[a]

[a] L. Yüceer, *Carbohydr. Res.*, **56**, 87 (1977).

8. Cyclopentylidene Ketal:  , **8**

9. Cyclohexylidene Ketal:  , **9**

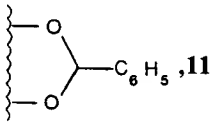
10. Cycloheptylidene Ketal:  , **10**

Compounds **8, 9,** and **10** can be prepared by an acid-catalyzed reaction of a diol and the cycloalkanone in the presence of ethyl orthoformate and mesitylenesulfonic acid.[a]

The relative ease of acid-catalyzed hydrolysis [0.53 *M* H_2SO_4/H_2O–PrOH (65:35), 20°] for compounds **8, 10, 6,** and **9** is $C_5 \sim C_7 > C_3$ (acetonide) >> C_6 (e.g., $t_{1/2}$ for 1,2-*O*-alkylidene-α-D-glucopyranoses of C_5, C_7, C_3 acetonide, and C_6 derivatives are 8, 10, 20, and 124 h, respectively).[a]

Compound **9** can also be prepared from a diol and 1-(trimethylsiloxy)cyclohexene (concd HCl, 20°, 10–30 min, 70–75% yield)[b] and cleaved by acidic hydrolysis (10% HCl/Et_2O, 25°, 5 min[b]; CF_3CO_2H/H_2O, 20°, 6 min to 2 h, 65–85% yield[c]).

[a] W. A. R. van Heeswijk, J. B. Goedhart, and J. F. G. Vliegenthart, *Carbohydr. Res.*, **58**, 337 (1977).
[b] G. L. Larson and A. Hernandez, *J. Org. Chem.*, **38**, 3935 (1973).
[c] S. L. Cook and J. A. Secrist, *J. Am. Chem. Soc.*, **101**, 1554 (1979).

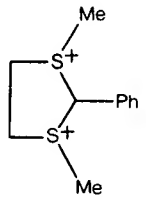
11. Benzylidene Acetal:  , **11**

Formation

(1) sugar $\xrightarrow[28°,\ 4\ h]{PhCHO/ZnCl_2[a]}$ **11**

(2) glucose osazone $\xrightarrow[25°,\ 4\ h]{PhCHO/DMSO,\ concd\ H_2SO_4[b]}$ **11**

In DMSO a dioxane derivative of the sugar, formed kinetically, is converted to the thermodynamically more stable dioxolane.[b]

(3) diol +  $\xrightarrow[25°,\ 16\ h,\ 45–82\%]{K_2CO_3\ or\ Py,\ CH_2Cl_2[c]}$ **11**

diol = 1,2-, 1,3-, or 1,4-compound

Cleavage

(1) **11** $\xrightarrow[25°,\ 30–45\ min,\ 90\%]{H_2/Pd\text{-}C,\ HOAc[d]}$ diol

(2) **11** $\xrightarrow[85\%]{Na/NH_3[e]}$ *N*-acetylglucosamine

(3) Compound **11** is cleaved by acidic hydrolysis (e.g., 0.01 *N* H_2SO_4, 100°, 3 h, 92% yield[f]; 80% HOAc, 25°, $t_{1/2}$ for uridine = 60 h[g]), conditions that do not cleave a methylenedioxy group.[f]

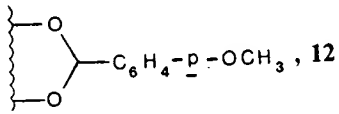
(4) **11** $\xrightarrow{-2.9\ \text{V},\ R_4N^+X^-,\ \text{DMF}^h}$ sugar

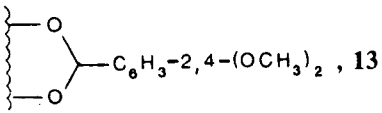
(5) **11** $\xrightarrow[25°,\ 8\ \text{h},\ 80\%]{Ph_3C^+BF_4^-,\ CH_3CN^i}$ 1:1 mixture of diol monobenzoates

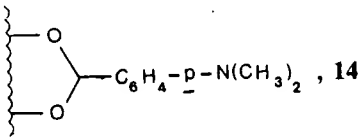
An acetonide is stable to these cleavage conditions.[i]

(6) A benzylidene acetal is cleaved in 100% yield by boron trichloride, a reagent that cleaves a variety of groups including acetonides.[j]

[a] H. G. Fletcher, Jr., *Methods Carbohydr. Chem.*, **II**, 307 (1963).
[b] R. M. Carman and J. J. Kibby, *Aust. J. Chem.*, **29**, 1761 (1976).
[c] R. M. Munavu and H. H. Szmant, *Tetrahedron Lett.*, 4543 (1975).
[d] W. H. Hartung and R. Simonoff, *Org. React.*, **7**, 263–326; see pp. 271, 284, 302 (1953).
[e] M. Zaoral, J. Ježek, R. Straka, and K. Masek, *Collect. Czech. Chem. Commun.*, **43**, 1797 (1978).
[f] R. M. Hann, N. K. Richtmyer, H. W. Diehl, and C. S. Hudson, *J. Am. Chem. Soc.*, **72**, 561 (1950).
[g] M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, *J. Am. Chem. Soc.*, **84**, 430 (1962).
[h] V. G. Mairanovsky, *Angew. Chem., Inter. Ed. Engl.*, **15**, 281 (1976).
[i] S. Hanessian and A. P. A. Staub, *Tetrahedron Lett.*, 3551 (1973).
[j] T. G. Bonner, E. J. Bourne, and S. McNally, *J. Chem. Soc.*, 2929 (1960).

12. *p*-Methoxybenzylidene Acetal:  , **12**

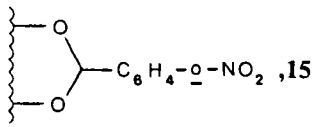
13. 2,4-Dimethoxybenzylidene Acetal:  , **13**

14. *p*-Dimethylaminobenzylidene Acetal:  , **14**

Compounds **12**[a] and **13**[b] were prepared, by reaction with the methoxybenzaldehyde (acid cat., 70–95% yield), to protect the 2′,3′-diol system in nucleosides. Compounds **12** and **13** are cleaved by very mild acidic hydrolysis: **12**, 80% HOAc, 25°, 10 h, 100% cleaved (10 times faster than an *O*-benzylidene acetal[a]); **13**, 80% HOAc, 25° or 90% CF_3CO_2H, 30°, 2–10 min, good yield.[b]

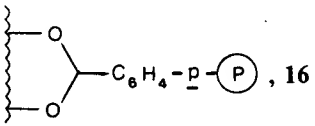
Compound **14**,[b] like compounds **12** and **13**, was prepared (by reaction with 4-*N*,*N*-dimethylaminobenzaldehyde, acid cat., 25°, 24 h, 55–80% yield) to protect the 2′,3′-diol system in nucleosides. Compound **14** is cleaved in good yield by acidic hydrolysis (e.g., 80% HOAc, 25° or 90% CF_3CO_2H, 30°, 2–10 min).[b]

[a] M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, *J. Am. Chem. Soc.*, **84**, 430 (1962).
[b] F. Cramer, W. Saenger, K.-H. Scheit, and J. Tennigkeit, *Liebigs Ann. Chem.*, **679**, 156 (1964).

15. *o*-Nitrobenzylidene Acetal:  , **15**

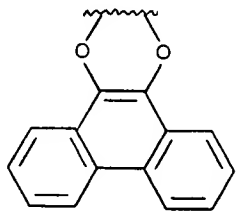
Compound **15**, prepared to protect a *cis*-1,2-diol in a sugar, has been cleaved in 88% yield by irradiation. Cleavage of a *m*- or *p*-nitro derivative by irradiation could not be effected.[a]

[a] P. M. Collins and N. N. Oparaeche, *J. Chem. Soc., Chem. Commun.*, 532 (1972).

16. *p*-(P)-Benzylidene Acetal:  , **16**

Compound **16** was prepared by reaction with a polymer-bound benzaldehyde ((P) = divinylbenzene-styrene copolymer)/TsOH, 89% yield, from the C_4,C_6-hydroxyl groups in sucrose, and cleaved by acidic hydrolysis (CF_3CO_2H-dioxane, 70–80% yield).[a]

[a] J.M.J.M. Fréchet and G. Pellé, *J. Chem. Soc., Chem. Commun.*, 225 (1975).

17. Phenanthrylidene Derivative:  , **17**

Compound **17** was prepared to protect a *cis*-1,2-diol in a sugar by reaction with 9,10-phenanthraquinone under irradiation (20°, C_6H_6, 15 h, ~50% yield). It is

cleaved by oxidation with ozone (−10°, 5 h) to the ester, followed by basic hydrolysis (NaOMe/$CHCl_3$, 0°, 12 h, 75% yield).[a]

[a] B. Helferich and E. von Gross, *Chem. Ber.*, **85**, 531 (1952); B. Helferich, E. N. Mulcahy, and H. Ziegler, *Chem. Ber.*, **87**, 233 (1954); B. Helferich and M. Gindy, *Chem. Ber.*, **87**, 1488 (1954).

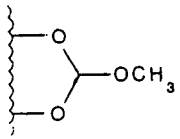
Cyclic Ortho Esters

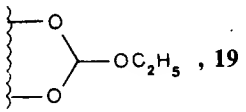
A variety of cyclic ortho esters,[a,b] including cyclic orthoformates, have been developed to protect *cis*-1,2-diols in nucleosides. Cyclic ortho esters are more readily cleaved by acidic hydrolysis (e.g., by a phosphate buffer, pH 4.5–7.5, or by 0.005–0.05 *M* HCl)[c] than are acetonides.

[a] C. B. Reese, *Tetrahedron*, **34**, 3143 (1978).

[b] V. Amarnath and A. D. Broom, *Chem. Rev.*, **77**, 183 (1977).

[c] M. Ahmad, R. G. Bergstrom, M. J. Cashen, A. J. Kresge, R. A. McClelland, and M. F. Powell, *J. Am. Chem. Soc.*, **99**, 4827 (1977).

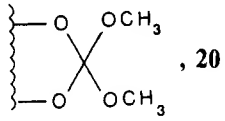
18. Methoxymethylene Acetal:  , **18**

19. Ethoxymethylene Acetal:  , **19**

Compounds **18**[a] and **19**[b] were prepared to protect *cis*-1,2-diols in nucleosides by reaction with trimethyl or triethyl orthoformate (acid catalyst, 77%, 45–80% yields, respectively). Compounds **18** and **19** are cleaved by mild acidic hydrolysis: **18**, 0.01 *N* HCl, 20°, 20 min, followed by basic hydrolysis of the resulting monoformates[a]; **19**, 0.01 *N* HCl, 20°, 10 min, or oxalic acid, warm, followed by basic hydrolysis.[b]

[a] B. E. Griffin, M. Jarman, C. B. Reese, and J. E. Sulston, *Tetrahedron*, **23**, 2301 (1967).

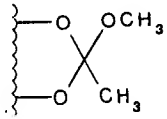
[b] J. Žemlička, *Chem. Ind. (London)*, 581 (1964); F. Eckstein and F. Cramer, *Chem. Ber.*, **98**, 995 (1965).

20. Dimethoxymethylene Ortho Ester:  , **20**

Compound **20** was prepared, by reaction with tetramethyl orthocarbonate (TsOH/dioxane, 42–82% yield), to protect the *cis*-1,2-diol system in nucleosides.

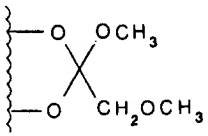
It is readily cleaved by acidic hydrolysis (0.01 *N* HCl, 20°, $t_{1/2}$ = 10 min; 98% HCOOH) to a cyclic carbonate that can then be cleaved by basic hydrolysis.[a]

[a] G. R. Niaz and C. B. Reese, *J. Chem. Soc., Chem. Commun.*, 552 (1969).

21. 1-Methoxyethylidene Ortho Ester:  , **21**

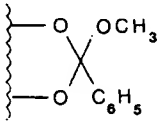
Compound **21** was prepared by acid-catalyzed transketalization [$MeC(OMe)_3$, TsOH, 55% yield] to protect the 1,2-diol system in nucleosides. It is very readily cleaved by acidic hydrolysis [1% HOAc (pH 3), 20°, 30 sec, 100% yield] to a mixture of mono 2′- and 3′-acetates.[a]

[a] C. B. Reese and J. E. Sulston, *Proc. Chem. Soc.*, 214 (1964).

22. 1,2-Dimethoxyethylidene Ortho Ester:  , **22**

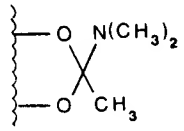
Compound **22** was prepared by acid-catalyzed transketalization [$MeOCH_2C(OMe)_3$, mesitylenesulfonic acid, DMF, 20°, 3–7 h, satisfactory yields] to protect 1,2-diols in nucleosides. It is cleaved by acidic hydrolysis (98% HCOOH, 25°, 30 min, 69% yield) to a mono methoxyacetate.[a]

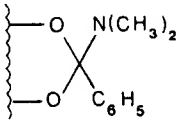
[a] J. H. van Boom, G. R. Owen, J. Preston, T. Ravindranathan, and C. B. Reese, *J. Chem. Soc. C*, 3230 (1971).

23. α-Methoxybenzylidene Ortho Ester:  , **23**

Compound **23** was prepared and cleaved by conditions similar to those described for compound **21**. Acidic hydrolysis gave a mixture of mono 2′- and 3′-benzoates.[a]

[a] C. B. Reese and J. E. Sulston, *Proc. Chem. Soc.*, 214 (1964).

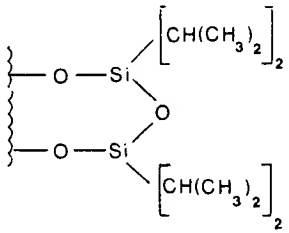
24. 1-(*N*,*N*-Dimethylamino)ethylidene Derivative:  , **24**

25. α-(*N,N*-Dimethylamino)benzylidene Derivative:  , **25**

Compounds **24**[a] and **25**[a] were prepared in high yields from *cis*-1,2-diols and $CH_3C(OMe)_2NMe_2$ or $PhC(OMe)_2NMe_2$, respectively. They are readily cleaved by hydrolysis (3% MeOH–H_2O, 20° or reflux, 100% yield of diol; dil HOAc, 1 : 1 mixture of mono 2- and 3-acetates or benzoates).

[a] S. Hanessian and E. Moralioglu, *Can. J. Chem.*, **50**, 233 (1972).

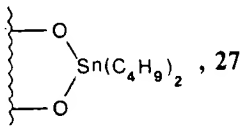
26. 1,3-(1,1,3,3-Tetraisopropyldisiloxanylidene) Derivative:

 , **26**

The author wished to protect, simultaneously, the 3′- and 5′-hydroxyl groups in nucleosides. 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane [$ClSi(i\text{-}Pr)_2OSi(i\text{-}Pr)_2Cl$] reacts first with the primary 5′-hydroxyl group, then intramolecularly with the 3′-hydroxyl group to form compound **26** in 70–80% yield. The reagent will react with a 2′,3′-diol system in a nucleoside. Compound **26** is stable to 0.3 *M* TsOH/dioxane, 10% $CF_3CO_2H/CHCl_3$, 5 *M* NH_3/dioxane–H_2O, and Et_3N or pyridine. It is cleaved by a variety of conditions: *n*-$Bu_4N^+F^-$, THF, 10 min; *n*-$Bu_3\overset{+}{N}HF^-$, 2 h; 0.2 *M* HCl/dioxane–H_2O, 24 h; 0.2 *M* HCl/MeOH, 9 h; and 0.2 *M* NaOH/dioxane–H_2O, 1 week.

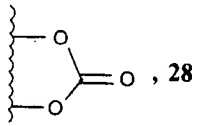
Selective cleavage at the 3′-position was effected by reaction with 0.2 *M* NaOH/dioxane–H_2O, 20°, 95% yield or *n*-$Bu_3\overset{+}{N}HF^-$/THF, 20°, 60% yield. Attempted cleavage at the 5′-position (with 0.2 *M* HCl/dioxane–H_2O) gave a mixture of products: 2′-OTIPDSi[x]: 3′-OTIPDSi[x]: 5′-OTIPDSi[x] (3 : 5 : 2), [TIPDSi[x] = $HOSi(i\text{-}Pr_2)_2OSi(i\text{-}Pr)_2$-].[a]

[a] W. T. Markiewicz, *J. Chem. Res. Synop.*, 24 (1979).

27. Stannoxane Derivative:  , **27**

Compound **27** was prepared from a 1,2- or 1,3-diol by reaction with dibutyltin oxide. Reaction of compound **27** with 1 eq of benzoyl chloride or toluenesulfonyl chloride converts one of the hydroxyl groups to a benzoate or toluenesulfonate.[a]

[a] A. Shanzer, *Tetrahedron Lett.*, **21**, 221 (1980).

28. Cyclic Carbonates:  , **28**

Cyclic carbonates,[a,b] prepared from 1,2- and 1,3-diols and phosgene or a chloroformate, are stable to the acid conditions that hydrolyze an acetonide (H_2SO_4, MeOH, 45°, 5 h).[c] They are readily cleaved by basic hydrolysis.

Formation

(1) diol + Cl_2CO $\xrightarrow[1\text{ h}]{\text{Py, 20°}^d}$ **28**

(2) 1,2-diol + $ClCO_2C_6H_4$-*p*-NO_2 $\xrightarrow[20°,\ 5\text{ days, }72\%]{\text{Py}^e}$ **28**

(3) diol + *N,N*′-carbonyldiimidazole $\xrightarrow[12\text{ h to 4 days, }90\%]{C_6H_6,\ \text{heat}^f}$ **28**

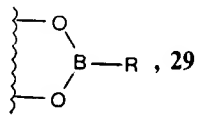
Cleavage

(1) **28** $\xrightarrow[70°]{Ba(OH)_2{}^g}$ 1,2-diol

(2) **28** $\xrightarrow[\text{reflux, 15 min, }100\%]{\text{aq Py}^e}$ uridine

(3) **28** $\xrightarrow[25°,\ 5\text{ min, }100\%]{0.5\ M\ \text{NaOH/50\% aq dioxane}^e}$ uridine

[a] L. Hough, J. E. Priddle, and R. S. Theobald, *Adv. Carbohydr. Chem.*, **15**, 91–158 (1960).
[b] V. Amarnath and A. D. Broom, *Chem. Rev.*, **77**, 183 (1977).
[c] W. N. Haworth and C. R. Porter, *J. Chem. Soc.*, 2796 (1929).
[d] W. N. Haworth and C. R. Porter, *J. Chem. Soc.*, 151 (1930).
[e] R. L. Letsinger and K. K. Ogilvie, *J. Org. Chem.*, **32**, 296 (1967).
[f] J. P. Kutney and A. H. Ratcliffe, *Synth. Commun.*, **5**, 47 (1975).
[g] W. G. Overend, M. Stacey, and L. F. Wiggins, *J. Chem. Soc.*, 1358 (1949).

29. Cyclic Boronates:  , **29**

30. Phenyl Boronate: 29, R = C_6H_5

31. *p*-Ⓟ-Phenyl Boronate: 29, R = *p*-Ⓟ-C_6H_4

Cyclic boronates have been used to a limited extent (because they are hydrolyzed very readily) to protect diols in carbohydrates[a] and nucleosides. Cyclic boronates that have been isolated from aqueous solutions may have been insoluble rather than stable.[a] Ethyl boronates have been studied extensively,[b] but are liquids and provide less satisfactory protection.

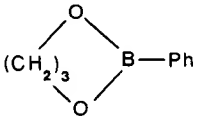
Formation

$$\text{diol} + \text{R-B(OH)}_2 \xrightarrow{C_6H_6[c] \text{ or Py}[d]} \textbf{30 or 31}$$

30, R = Ph, 90% yield[c]

31, R = *p*-Ⓟ-C_6H_4[d]

Cleavage

(1) **30** $\xrightarrow{HO(CH_2)_3OH, \text{ acetone}[a]}$ diol + 

(2) **31** $\xrightarrow[30 \text{ min, } 83\%]{Me_2CO\text{-}H_2O\ (4:1)[d]}$ diol

[a] R. J. Ferrier, *Adv. Carbohydr. Chem. Biochem.*, **35**, 31–80 (1978).
[b] W. V. Dahlhoff and R. Köster, *J. Org. Chem.*, **41**, 2316 (1976), and references cited therein.
[c] R. J. Ferrier, *Methods Carbohydr. Chem.*, **VI**, 419–426 (1972).
[d] J. M. J. Fréchet, L. J. Nuyens, and E. Seymour, *J. Am. Chem. Soc.*, **101**, 432 (1979).

3

Protection for Phenols and Catechols

*Included in Reactivity Chart 4.